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Multiple Comparisons in Nonlinear Repeated Measurements

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Abstract

It is interest to compare functions of parameters in nonlinear models for repeated measurements. In a pharmacokinetic model, the maximum value of the model would be a nonlinear function of some unknown parameters. In this paper, simultaneous confidence intervals of functions of parameters in a nonlinear model for repeated mesurement data are considered to compare the populations.

Key words: Confidence interval; Nonlinear model; Pairwise comparison; Repeated measurement.

1. Introduction

Let $\boldsymbol{y}_{ir} = (y_{ir,1}, \ldots, y_{ir,p})'$ be a p dimensional observation from the i-th population $(i = 1, \ldots, k,\ r = 1, \ldots, n_i)$. The element $y_{ir,j}$ is measured at time point t_j for the r-th observation from the i-th population, say $\boldsymbol{y}_{ir}$ is a repeated measurement data. For each element $y_{ir,j}$, we assume

$$y_{ir,j} = f(t_j; \boldsymbol{\beta}_i) + \varepsilon_{ir,j}\,,$$

where f is a known (nonlinear) function, $\varepsilon_{ir,j}$ is the error, and $\boldsymbol{\beta}_i = (\beta_{i1}, \ldots, \beta_{iq})'$ is unknown parameter $(q \leq p)$. Let $\boldsymbol{f}_i = (f(t_1; \boldsymbol{\beta}_i), \ldots, f(t_p; \boldsymbol{\beta}_i))'$, then $\boldsymbol{y}_{ir} = \boldsymbol{f}_i + \boldsymbol{\varepsilon}_{ir}$, where $\boldsymbol{\varepsilon}_{ir} = (\varepsilon_{ir,1}, \ldots, \varepsilon_{ir,p})'$. Suppose that $E[\boldsymbol{\varepsilon}_{ir}] = \mathbf{0}$, Var $[\boldsymbol{\varepsilon}_{ir}] = \boldsymbol{\Sigma}$, which is a positive definite, and $\boldsymbol{\varepsilon}_{ir}$'s are independent. Let $g_i = g(\boldsymbol{\beta}_i)$ be a nonlinear function of parameter $\boldsymbol{\beta}_i$. Our goal is to construct simultaneous confidence intervals for all-pairwise differences $g_i - g_{i'}$, $i \neq i'$. For linear models, SEO and KANDA (1996) gave simultaneous confidence intervals for multiple comparisons in a generalized multivariate analysis of variance model. In Section 2, the simultaneous confidence intervals are derived by a similar fashion using the linear Taylor expansion. Confidence intervals for nonlinear functions of parameters by the linear Taylor expansion in nonlinear regression are summarized in SEBER and WILD

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(1989). In Section 3, the accuracy of approximation by Taylor expansion is examined by simulation. A numerical example is given in Section 4.

A nonlinear model

$$\frac{\beta_1}{\beta_2 - \beta_3}\,(e^{-\beta_3 t} - e^{-\beta_2 t})\,, \qquad (\beta_2 > \beta_3)$$

is usually used for pharmacokinetic data, where β_1, β_2 and β_3 are unknown parameters, see e.g. LINDSEY et. al. (2000) or Section 5.5 of DAVIDIAN and GILTINAN (1995). In this model, β_2 and β_3 are the absorption and elimination rate parameters, respectively. If $\beta_3 \to \beta_2$, then the model tends to $\beta_1 t e^{-\beta_2 t}$. For each population, if the model is assumed that

$$f(t; \boldsymbol{\beta}_i) = \beta_{i1} t e^{-\beta_{i2} t}\,. \tag{1.1}$$

then our interest is the maximum value of this model. Hence we would like to compare

$$g_i = g(\boldsymbol{\beta}_i) = \max_t\, f(t; \boldsymbol{\beta}_i) = \frac{\beta_{i1}}{\beta_{i2}}\, e^{-1}, \tag{1.2}$$

by constructing the simultaneous confidence intervals of the differences.

For the growth model, the logistic model

$$f(t; \boldsymbol{\beta}_i) = \frac{\beta_{i0}}{1 + \beta_{i1} e^{-\beta_{i2} t}}\,, \tag{1.3}$$

is often used, see e.g. LINDSEY (2001). In this model, we are interested in comparing the inflection points, that is

$$g_i = \frac{\log \beta_{i1}}{\beta_{i2}}\,, \tag{1.4}$$

which is obtained by solving $\mathrm{d}^2 f/\mathrm{d}t^2 = 0$ with respect to t.

2. Simultaneous confidence intervals for differences

For estimation of the parameters $\boldsymbol{\beta}_i$, we use the ordinary least squares estimators $\hat{\boldsymbol{\beta}}_i$, which is minimizes $\sum_r (\boldsymbol{y}_{ir} - \boldsymbol{f}_i)' (\boldsymbol{y}_{ir} - \boldsymbol{f}_i)$. Let

$$\boldsymbol{V}_i = \sum_r (\boldsymbol{y}_{ir} - \hat{\boldsymbol{f}}_i)\, (\boldsymbol{y}_{ir} - \hat{\boldsymbol{f}}_i)'\,,$$

where $\hat{\boldsymbol{f}}_i = (f(t_1; \hat{\boldsymbol{\beta}}_i), \ldots, f(t_p; \hat{\boldsymbol{\beta}}_i))'$. By the linear Taylor expansion, the estimates of $\boldsymbol{f}_i$ and g_i are approximated by

$$\hat{\boldsymbol{f}}_i = \boldsymbol{f}(\hat{\boldsymbol{\beta}}_i) \approx \boldsymbol{f}(\boldsymbol{\beta}_i) + \boldsymbol{F}_{\cdot}^{(i)} (\hat{\boldsymbol{\beta}}_i - \boldsymbol{\beta}_i) \tag{2.1}$$

and

$$\hat{g}_i = g(\hat{\boldsymbol{\beta}}_i) \approx g(\boldsymbol{\beta}_i) + \boldsymbol{g}'_{i\cdot}(\hat{\boldsymbol{\beta}}_i - \boldsymbol{\beta}) , \tag{2.2}$$

respectively, where

$$\boldsymbol{F}^{(i)}_{\cdot} = \left(\frac{\partial \boldsymbol{f}_i}{\partial \boldsymbol{\beta}'_i}\right) = \begin{pmatrix} \dfrac{\partial f(t_1, \boldsymbol{\beta}_i)}{\partial \beta_{i1}} & \cdots & \dfrac{\partial f(t_1, \boldsymbol{\beta}_i)}{\partial \beta_{iq}} \\ \vdots & & \vdots \\ \dfrac{\partial f(t_p, \boldsymbol{\beta}_i)}{\partial \beta_{i1}} & \cdots & \dfrac{\partial f(t_p, \boldsymbol{\beta}_i)}{\partial \beta_{iq}} \end{pmatrix}$$

and

$$\boldsymbol{g}'_{i\cdot} = \left(\frac{\partial g_i}{\partial \beta_{i1}}, \dots, \frac{\partial g_i}{\partial \beta_{iq}}\right).$$

By (2.1) and (2.2), $\hat{\boldsymbol{\beta}}_i - \boldsymbol{\beta}_i \approx (\boldsymbol{F}^{(i)'}_{\cdot}\boldsymbol{F}^{(i)}_{\cdot})^{-1}\, \boldsymbol{F}^{(i)'}_{\cdot}\sum_r \boldsymbol{\varepsilon}_{ir}/n_i$, $g(\hat{\boldsymbol{\beta}}_i) - g(\boldsymbol{\beta}_i) \approx \boldsymbol{g}'_{i\cdot}(\hat{\boldsymbol{\beta}}_i - \boldsymbol{\beta}_i)$ and

$$\begin{aligned} \boldsymbol{V}_i &= \sum_r (\boldsymbol{y}_{ir} - \hat{\boldsymbol{f}}_i)\, (\boldsymbol{y}_{ir} - \hat{\boldsymbol{f}}_i)' \\ &\approx \sum_r \{\boldsymbol{\varepsilon}_{ir} - \boldsymbol{F}^{(i)}_{\cdot}(\hat{\boldsymbol{\beta}}_i - \boldsymbol{\beta}_i)\}\, \{\boldsymbol{\varepsilon}_{ir} - \boldsymbol{F}^{(i)}_{\cdot}(\hat{\boldsymbol{\beta}}_i - \boldsymbol{\beta}_i)\}' \\ &\approx \sum_r (\boldsymbol{\varepsilon}_{ir} - \bar{\boldsymbol{\varepsilon}}_i)(\boldsymbol{\varepsilon}_{ir} - \bar{\boldsymbol{\varepsilon}}_i)' + n_i(\boldsymbol{I}_p - \boldsymbol{P}_{F_i})\, \bar{\boldsymbol{\varepsilon}}_i\bar{\boldsymbol{\varepsilon}}'_i(\boldsymbol{I}_p - \boldsymbol{P}_{F_i})' , \end{aligned}$$

where $\bar{\boldsymbol{\varepsilon}}_i = \sum_r \boldsymbol{\varepsilon}_{ir}/n_i$ and $\boldsymbol{P}_{F_i} = \boldsymbol{F}^{(i)}_{\cdot}(\boldsymbol{F}^{(i)'}_{\cdot}\boldsymbol{F}^{(i)}_{\cdot})^{-1}_{\cdot}\, \boldsymbol{F}^{(i)'}_{\cdot}$. If $\boldsymbol{\varepsilon}_{ir}$ has the p-variate normal distribution, $N_p(\boldsymbol{0}, \boldsymbol{\Sigma})$, then $(\boldsymbol{F}^{(i)'}_{\cdot}\boldsymbol{F}^{(i)}_{\cdot})^{-1}\, \boldsymbol{F}^{(i)'}_{\cdot} \sum_r \boldsymbol{\varepsilon}_{ir}/n_i$ has the k-variate normal distribution, $N_k(\boldsymbol{0}, (\boldsymbol{F}^{(i)'}_{\cdot}\boldsymbol{F}^{(i)}_{\cdot})^{-1}\, \boldsymbol{F}^{(i)'}_{\cdot}\boldsymbol{\Sigma}\boldsymbol{F}^{(i)}_{\cdot}\ (\boldsymbol{F}^{(i)'}_{\cdot}\boldsymbol{F}^{(i)}_{\cdot})^{-1}/n_i)$, and $\boldsymbol{g}'_{i\cdot}(\hat{\boldsymbol{\beta}}_i - \boldsymbol{\beta}_i)$ has $N(0,\ \boldsymbol{g}'_{i\cdot}(\boldsymbol{F}^{(i)'}_{\cdot}\boldsymbol{F}^{(i)}_{\cdot})^{-1}\, \boldsymbol{F}^{(i)'}_{\cdot}\boldsymbol{\Sigma}\boldsymbol{F}^{(i)}_{\cdot}(\boldsymbol{F}^{(i)'}_{\cdot}\boldsymbol{F}^{(i)}_{\cdot})^{-1}\, \boldsymbol{g}_{i\cdot}/n_i)$. The statistics $\hat{\boldsymbol{\beta}}_i$ and $\boldsymbol{V}_i$ are approximately independent. Even if the distribution of $\boldsymbol{\varepsilon}_{ir}$ is not normal, $\bar{\boldsymbol{\varepsilon}}_i$ has a normal distribution approximately under the large sample. Note that $\boldsymbol{F}^{(i)'}_{\cdot}(\boldsymbol{I}_p - \boldsymbol{P}_{F_i}) = \boldsymbol{O}$, $\boldsymbol{F}^{(i)'}_{\cdot}\boldsymbol{V}_i\boldsymbol{F}^{(i)}_{\cdot}$ has a Wishart distribution with covariance matrix $\boldsymbol{F}^{(i)'}_{\cdot}\boldsymbol{\Sigma}\boldsymbol{F}^{(i)}_{\cdot}$ and $n_i - 1$ degrees of freedom, $W_k(\boldsymbol{F}^{(i)'}_{\cdot}\boldsymbol{\Sigma}\boldsymbol{F}^{(i)}_{\cdot},\ n_i - 1)$, approximately. Hence the distribution of $\boldsymbol{V} = \boldsymbol{V}_1 + \ldots + \boldsymbol{V}_k$ would be approximated by $W_p(\boldsymbol{\Sigma},\ \nu)$, where $\nu = n_1 + \ldots + n_k - k$. So, $\boldsymbol{S} = \boldsymbol{V}/\nu$ is an estimate of $\boldsymbol{\Sigma}$ and $\boldsymbol{a}'_i\boldsymbol{V}\boldsymbol{a}_i/\boldsymbol{a}'_i\boldsymbol{\Sigma}\boldsymbol{a}_i$ has a chi-square distribution with ν degrees of freedom, χ^2_ν, approximately, where $\boldsymbol{a}_i = \boldsymbol{F}^{(i)}_{\cdot}(\boldsymbol{F}^{(i)'}_{\cdot}\boldsymbol{F}^{(i)}_{\cdot})^{-1}\, \boldsymbol{g}_{i\cdot}$.

In order to compare g_i, we propose the following simultaneous confidence intervals for all pairwise differences:

$$g_i - g_{i'} \in \hat{g}_i - \hat{g}_{i'} \pm q\, \sqrt{\boldsymbol{a}'_i\boldsymbol{S}\boldsymbol{a}_i/n_i + \boldsymbol{a}'_{i'}\boldsymbol{S}\boldsymbol{a}_{i'}/n_{i'}} \quad \text{for all} \quad i \neq i', \tag{2.3}$$

where q is the solution to the equation

$$P\left(\frac{\sqrt{\nu}\,|(\hat{g}_i - \hat{g}_{i'}) - (g_i - g_{i'})|}{\sqrt{\boldsymbol{a}_i' \boldsymbol{V} \boldsymbol{a}_i / n_i + \boldsymbol{a}_{i'}' \boldsymbol{V} \boldsymbol{a}_{i'} / n_{i'}}} < q, \text{ for all } i \neq i'\right)$$

$$= E_V\left[P\left(\frac{|(\hat{g}_i - \hat{g}_{i'}) - (g_i - g_{i'})|}{\sqrt{\boldsymbol{a}_i' \boldsymbol{\Sigma} a_i / n_i + \boldsymbol{a}_{i'}' \boldsymbol{\Sigma} \boldsymbol{a}_{i'} / n_{i'}}}\right.\right.$$

$$\left.\left. < \frac{q}{\sqrt{\nu}} \sqrt{\frac{\boldsymbol{a}_i' \boldsymbol{V} \boldsymbol{a}_i / n_i + \boldsymbol{a}_{i'} \boldsymbol{V} \boldsymbol{a}_{i'} / n_{i'}}{\boldsymbol{a}_i' \boldsymbol{\Sigma} \boldsymbol{a}_i / n_i + \boldsymbol{a}_{i'}' \boldsymbol{\Sigma} \boldsymbol{a}_{i'} / n_{i'}}}, \text{ for all } i \neq i' \;|V\right)\right] = 1 - \alpha. \qquad (2.4)$$

However, we can not solve the equation (2.4), because (2.4) depends on the unknown parameters, $\boldsymbol{\Sigma}$ and $\boldsymbol{a}_i$. Let $\boldsymbol{W} = \boldsymbol{\Sigma}^{-1/2} V \boldsymbol{\Sigma}^{-1/2}$ and $\boldsymbol{b}_i = \boldsymbol{\Sigma}^{1/2} \boldsymbol{a}_i / \sqrt{n_i}$, then

$$\frac{(\boldsymbol{a}_i' \boldsymbol{V} \boldsymbol{a}_i / n_i + \boldsymbol{a} \boldsymbol{V} \boldsymbol{a}_{i'}' i' / n_{i'})}{(\boldsymbol{a}_i' \boldsymbol{\Sigma} \boldsymbol{a}_i / n_i + \boldsymbol{a}_{i'}' \boldsymbol{\Sigma} \boldsymbol{a}_{i'} / n_{i'})} = \frac{(\boldsymbol{b}_i' \boldsymbol{W} \boldsymbol{b}_i + \boldsymbol{b}_{i'}' \boldsymbol{W} \boldsymbol{b}_{i'})}{(\boldsymbol{b}_i' \boldsymbol{b}_i + \boldsymbol{b}_{i'}' \boldsymbol{b}_{i'})} = w_{ii'}\,,$$

where $\boldsymbol{W}$ has $W_p(\boldsymbol{I}_p,\ \nu)$. If the all statistics $w_{ii'}$ are approximated by a same statistic w distributed as $\chi^2_{\nu^*}$, then $\sqrt{2}q$ would be approximated by the upper α point of a Studentized range distribution with k treatment and ν^* degrees of freedom. We wish to approximate ν^* by equating the second order Taylor expansion of moment generating functions of w/ν^* and $w_{ii'}/\nu$, which are

$$m_{w/\nu^*}(u) \approx 1 + u + (1 + 2/\nu^*)\, u^2\,,$$

and

$$m_{w_{ii'}/\nu}(u) \approx 1 + u + \left(1 + \frac{2\{(\boldsymbol{b}_i' \boldsymbol{b}_i)^2 + (\boldsymbol{b}_{i'}' \boldsymbol{b}_{i'})^2 + 2(\boldsymbol{b}_i' \boldsymbol{b}_{i'})^2\}}{\nu(\boldsymbol{b}_i' \boldsymbol{b}_i + \boldsymbol{b}_{i'}' \boldsymbol{b}_{i'})^2}\right) u^2\,,$$

respectively. The coefficient of u^2 in $m_{w_{ii'}/\nu}(u)$ is obtained by using Theorem 2.2.11 of Siotani, Hayakawa, and Fujikoshi (1985). Then an approximation of ν^* would be obtained by $m_{w/\nu^*}(u) = m_{w_{ii'}/\nu}(u)$, whose solution is different for each pair (i, i'). But we find that

$$\nu^* = \frac{(\boldsymbol{b}_i' \boldsymbol{b}_i + \boldsymbol{b}_{i'}' \boldsymbol{b}_{i'})^2}{(\boldsymbol{b}_i' \boldsymbol{b}_i)^2 + (\boldsymbol{b}_{i'}' \boldsymbol{b}_{i'})^2 + 2(\boldsymbol{b}_i' \boldsymbol{b}_{i'})^2}\, \nu \geq \nu, \qquad (2.5)$$

by Schwarz inequality. In order to approximate q in (2.3), we use Studentized range distribution with k treatment and ν degrees of freedom. However, $\boldsymbol{a}_i = \boldsymbol{F}^{(i)}_{\cdot} (\boldsymbol{F}^{(i)'}_{\cdot} \boldsymbol{F}^{(i)}_{\cdot})^{-1}\, \boldsymbol{g}_{i\cdot}$ in (2.3) includes unknown parameter $\boldsymbol{\beta}_i$. So, the unknown parameter should be replaced by $\hat{\boldsymbol{\beta}}_i$ for practical use.

3. Simulation

In the previous section, we gave the simultaneous confidence intervals for all pairwise comparison. The intervals are approximated by using Taylor expansion for the nonlinear model. In this section, we examine the accuracy of the approximation by simulation. A special case of the pharmacokinetic model (1.1) and the logistic model (1.3) are used in the simulation. We compare the maximum values (1.2) in the model (1.1) and compare the inflection points (1.4) in the model (1.3) with known $\beta_{i0} = 1$. We choose the parameters for 3 and 4 populations ($k = 3, 4$) as follows:

Table 1

Models and Parameters

$f(t; \boldsymbol{\beta}_i) = \beta_{i1} t e^{-\beta_{i2} t}$, $(g_i = \beta_{i1} e^{-1}/\beta_{i2})$

Population	1	2	3	4
β_{i1}	0.8	0.9	1.0	0.8
β_{i2}	0.6	0.5	0.4	0.4

$f(t; \boldsymbol{\beta}_i) = (1 + \beta_{i1} e^{-\beta_{i2} t})^{-1}$, $(g_i = (\log \beta_{i1})/\beta_{i2})$

Population	1	2	3	4
β_{i1}	2.0	2.4	3.0	2.8
β_{i2}	1.5	1.2	1.0	1.4

The observed points are $t = 1, 2, 3, 4$ $(p = 4)$ for both models and the sample sizes from each population are $n_i = 5, 8, 12, 16$ $(i = 1, 2, 3, 4)$. For $k = 3$, we exclude the 4th population $(i = 4)$ in simulation. The error has the normal distribution with mean and covariance matrix $\boldsymbol{\Sigma}_\ell$ $(\ell = 1, 2, 3, 4)$, where

$$\boldsymbol{\Sigma}_1 = 0.1^2 \boldsymbol{I},\ \boldsymbol{\Sigma}_2 = \text{diag}\ (0.08^2, 0.10^2, 0.10^2, 0.08^2)$$

for model (1.1) and

$$\boldsymbol{\Sigma}_3 = 0.05^2 \boldsymbol{I},\ \boldsymbol{\Sigma}_4 = \text{diag}\ (0.05^2, 0.05^2, 0.04^2, 0.04^2)$$

for model (1.3). We also examine about $g_i = \beta_{i2}$ for the model (1.1) with $\boldsymbol{\Sigma}_1$ and for the model (1.3) with $\boldsymbol{\Sigma}_3$ when $k = 3$. For these values and $\alpha = 0.05$, 10,000 pairwise intervals are constructed. The proportion, that 3 pairwise confidence intervals (2.3) include the true values $g_i - g_{i'}$, is calculated. The results are in Table 2. Values in the parentheses ( ) in Table 2 are the proportion, that (2.3) include the true values, when the value of $\lim_{\nu\to\infty} q$ is used instead of the percentile point q of the Studentized range distribution with k treatment and ν degrees of freedom. The values of q and $\lim_{\nu\to\infty} q$ are tabulated in HSU (1996).

From Table 2, almost all values are greater than 0.95, that is the proposed intervals are conservative. This would be caused by (2.5). If we use the asymptotic percentile point $\lim_{\nu\to\infty} q$, the approximation would be good under the large sample size ($n_i = 16$). But the confidence level by using $\lim_{\nu\to\infty} q$ is less than 0.95 under

Table 2
Accuracy of Approximation

i) $g_i = \beta_{i1}e^{-1}/\beta_{i2}$ in model (1.1)

k	$\boldsymbol{\Sigma}$	n_i			
		5	8	12	16
3	$\boldsymbol{\Sigma}_1$	0.9533	0.9528	0.9545	0.9508
		(0.9194)	(0.9320)	(0.9420)	(0.9408)
3	$\boldsymbol{\Sigma}_2$	0.9526	0.9522	0.9518	0.9532
		(0.9147)	(0.9298)	(0.9410)	(0.9445)
4	$\boldsymbol{\Sigma}_1$	0.9516	0.9555	0.9516	0.9501
		(0.9166)	(0.9351)	(0.9378)	(0.9418)
4	$\boldsymbol{\Sigma}_2$	0.9491	0.9511	0.9508	0.9512
		(0.9141)	(0.9317)	(0.9376)	(0.9419)

ii) $g_i = (\log \beta_{i1})/\beta_{i2}$ in model (1.3)

k	$\boldsymbol{\Sigma}$	n_i			
		5	8	12	16
3	$\boldsymbol{\Sigma}_3$	0.9623	0.9616	0.9616	0.9587
		(0.9308)	(0.9364)	(0.9468)	(0.9483)
3	$\boldsymbol{\Sigma}_4$	0.9640	0.9613	0.9600	0.9567
		(0.9322)	(0.9448)	(0.9422)	(0.9470)
4	$\boldsymbol{\Sigma}_3$	0.9672	0.9651	0.9586	0.9590
		(0.9372)	(0.9451)	(0.9468)	(0.9505)
4	$\boldsymbol{\Sigma}_4$	0.9647	0.9609	0.9609	0.9568
		(0.9341)	(0.9427)	(0.9483)	(0.9492)

iii) $g_i = \beta_{i2}$ in models (1.1) and (1.3) when $k = 3$

Model	$\boldsymbol{\Sigma}$	n_i			
		5	8	12	16
(1.1)	$\boldsymbol{\Sigma}_1$	0.9542	0.9541	0.9513	0.9566
		(0.9194)	(0.9316)	(0.9386)	(0.9488)
(1.3)	$\boldsymbol{\Sigma}_3$	0.9615	0.9603	0.9587	0.9560
		(0.9332)	(0.9408)	(0.9474)	(0.9472)

the small sample size ($n_i = 5, 8$). We can not recommend to use $\lim_{\nu\to\infty} q$, when the sample size from each population is less than 8. When $k = 3$, the confidence levels for g_i of i) and iii) in the model (1.1) and for g_i of ii) and iii) in the model (1.3) are similar tendency, respectively. The confidence level would depend on the model rather than the function g_i. The maximum differences of simulation results and 0.95 are 0.0172 by the proposed procedure and 0.0359 by the limitting distribution. Our proposed procedure would be good approximation even if the sample sizes are small.

4. Numerical example

In this section, we give a numerical example by using a part of data in page 36 of DAVIS (2002). Tables 3.1, 3.2, and 3.3 display plasma inorganic phosphate measurements obtained from blood samples drawn 0.0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, and 5.0 hours after a standard-dose oral glucose challenge. We assume the model

$$f(t;\beta_i) = \beta_{i0} - \beta_{i1} t e^{-\beta_{i2} t}$$

Table 3.1
Control

	0.0	0.5	1.0	1.5	2.0	3.0	4.0	5.0
1	4.3	3.3	3.0	2.6	2.2	2.5	3.4	4.4
2	3.7	2.6	2.6	1.9	2.9	3.2	3.1	3.9
3	4.0	4.1	3.1	2.3	2.9	3.1	3.9	4.0
4	3.6	3.0	2.2	2.8	2.9	3.9	3.8	4.0
5	4.1	3.8	2.1	3.0	3.6	3.4	3.6	3.7
6	3.8	2.2	2.0	2.6	3.8	3.6	3.0	3.5
7	3.8	3.0	2.4	2.5	3.1	3.4	3.5	3.7
8	4.4	3.9	2.8	2.1	3.6	3.8	4.0	3.9

Table 3.2
Nonhyperinsulinemic obese

	0.0	0.5	1.0	1.5	2.0	3.0	4.0	5.0
1	4.3	3.3	3.0	2.6	2.2	2.5	2.4	4.9
2	5.0	4.9	4.1	3.7	3.7	4.1	4.7	4.9
3	4.6	4.4	3.9	3.9	3.7	4.2	4.8	5.0
4	4.3	3.9	3.1	3.1	3.1	3.1	3.6	4.0
5	3.1	3.1	3.3	2.6	2.6	1.9	2.3	2.7
6	4.8	5.0	2.9	2.8	2.2	3.1	3.5	3.6
7	3.7	3.1	3.3	2.8	2.9	3.6	4.3	4.4
8	5.4	4.7	3.9	4.1	2.8	3.7	3.5	3.7

Table 3.3
Hyperinsulinemic obese

	0.0	0.5	1.0	1.5	2.0	3.0	4.0	5.0
1	4.9	4.3	4.0	4.0	3.3	4.1	4.2	4.3
2	5.1	4.1	4.6	4.1	3.4	4.2	4.4	4.9
3	4.8	4.6	4.6	4.4	4.1	4.0	3.8	3.8
4	4.2	3.5	3.8	3.6	3.3	3.1	3.5	4.8
5	6.6	6.1	5.2	4.1	4.3	3.8	4.2	4.8
6	3.6	3.4	3.1	2.8	2.1	2.4	2.5	3.5
7	4.5	4.0	3.7	3.3	2.4	2.3	3.1	3.3
8	4.6	4.4	3.8	3.6	3.8	3.6	3.8	3.8

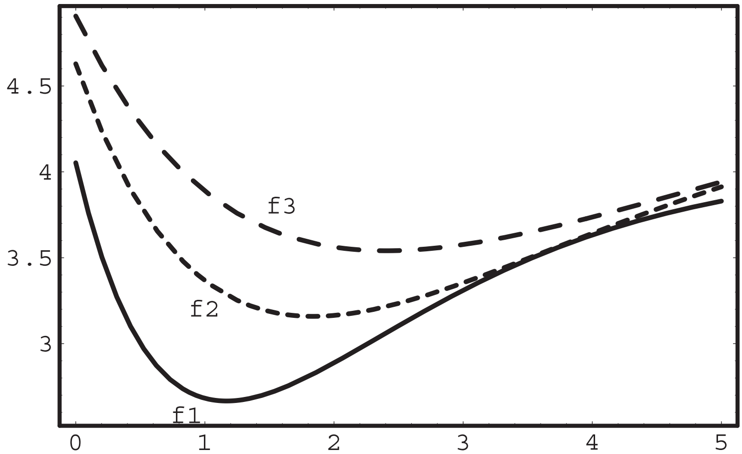

Fig. 1. Estimated Curves

for the data and construct simultaneous confidence intervals of $g_i - g_{i'}$, where $g_i = \beta_{0i} - e^{-1}\beta_{i1}/\beta_{i2}$, which is the minimum value of the model.

The estimates are calculated as follows:

$$f(t; \hat{\boldsymbol{\beta}}_1) = 4.053 - 3.227te^{-0.856t}, \qquad \hat{g}_1 = 2.667,$$
$$f(t; \hat{\boldsymbol{\beta}}_2) = 4.629 - 2.174te^{-0.544t}, \qquad \hat{g}_2 = 3.158,$$
$$f(t; \hat{\boldsymbol{\beta}}_3) = 4.907 - 1.545te^{-0.416t}, \qquad \hat{g}_3 = 3.542,$$

and

$$\boldsymbol{S} = \begin{pmatrix} 0.486 & 0.412 & 0.238 & 0.211 & 0.222 & 0.254 & 0.256 & 0.155 \\ 0.412 & 0.644 & 0.256 & 0.182 & 0.198 & 0.221 & 0.291 & 0.142 \\ 0.238 & 0.256 & 0.303 & 0.173 & 0.129 & 0.154 & 0.224 & 0.174 \\ 0.211 & 0.182 & 0.173 & 0.281 & 0.175 & 0.240 & 0.229 & 0.109 \\ 0.222 & 0.198 & 0.129 & 0.175 & 0.470 & 0.348 & 0.273 & 0.084 \\ 0.254 & 0.221 & 0.154 & 0.240 & 0.348 & 0.474 & 0.399 & 0.192 \\ 0.256 & 0.291 & 0.224 & 0.229 & 0.273 & 0.399 & 0.483 & 0.247 \\ 0.155 & 0.142 & 0.174 & 0.109 & 0.084 & 0.192 & 0.247 & 0.414 \end{pmatrix}.$$

The estimated curves are shown in Figure 1, in which $f_i = f(t; \hat{\boldsymbol{\beta}}_i)$, $(i = 1, 2, 3)$.

Let us take $\alpha = 0.05$, then $q = 2.521$, which is obtained from Table E.1 in Hsu (1996). Hence the simultaneous confidence intervals for all-pairwise differences are obtained in Table 4.

Table 4
Confidence Intervals

$g_1 - g_2$	-1.125,	0.143
$g_1 - g_3$	-1.519,	-0.231
$g_2 - g_3$	-1.028,	0.260

From Table 4, we find that the minimum values of the models for control and hyperinsulinemic obase (g_1 and g_3) are statistically different, and the values of (g_1 and g_2) and (g_2 and g_3) are not different.

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