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Nagahisa, Takeshi
Graduate School of Mathematics, Kyushu University

Hyakutake, Hiroto
Faculty of Mathematics, Kyushu University

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SIMULTANEOUS CONFIDENCE INTERVALS FOR PARAMETERS IN NONLINEAR MODELS OF REPEATED MEASUREMENTS

By

Takeshi NAGAHISA* and **Hiroto HYAKUTAKE†**

Abstract

It is interesting to compare populations whose samples are obtained by repeated measurements. In this paper, we wish to construct simultaneous confidence intervals for specified parameters in nonlinear models for repeated measurements. The confidence intervals are derived approximately by the first order linearization. A numerical example is also given.

Key Words and Phrases: first order linearization, nonlinear model, repeated measurements, simultaneous confidence intervals.

1. Introduction

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

$$y_{ir,j} = f(t_j; \boldsymbol{\beta}_{ir}) + \varepsilon_{ir,j}, \tag{1.1}$$

where f is a known (nonlinear) function, $\varepsilon_{ir,j}$ is the error, and $\boldsymbol{\beta}_{ir} = (\beta_{ir,1}, \cdots, \beta_{ir,q})'$ is unknown parameter ($q \leq p$). For example, such data arise in pharmacokinetics, growth processes, and so on; see Davidian and Giltinan (1995) or Vonesh and Chinchilli (1997). Let $\boldsymbol{f}(\boldsymbol{t}, \boldsymbol{\beta}_{ir}) = (f(t_1; \boldsymbol{\beta}_{ir}), \cdots, f(t_p; \boldsymbol{\beta}_{ir}))'$, then

$$\boldsymbol{y}_{ir} = \boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\beta}_{ir}) + \boldsymbol{\varepsilon}_{ir}, \tag{1.2}$$

where $\boldsymbol{\varepsilon}_{ir} = (\varepsilon_{ir,1}, \cdots, \varepsilon_{ir,p})'$. Let $\boldsymbol{\beta}_{ir} = \boldsymbol{d}(\boldsymbol{\phi}_i, \boldsymbol{b}_{ir})$, where $\boldsymbol{\phi}_i$ is a vector of fixed effects and $\boldsymbol{b}_{ir}$ is a vector of random effects. We assume that $\boldsymbol{d}(\boldsymbol{\phi}_i, \boldsymbol{b}_{ir}) = \boldsymbol{\phi}_i + \boldsymbol{b}_{ir}$, that $\boldsymbol{\varepsilon}_{ir}$'s are independent and have the multinormal distribution with mean $\boldsymbol{0}$ and covariance matrix $\sigma_0^2 I_p$, that is $N(\boldsymbol{0}, \sigma_0^2 I_p)$, and that $\boldsymbol{b}_{ir}$'s are independent and have $N(\boldsymbol{0}, D)$. The error $\boldsymbol{\varepsilon}_{ir}$ and the random effect $\boldsymbol{b}_{ir}$ are independent. Then we wish to construct simultaneous confidence intervals for $\boldsymbol{a}'\boldsymbol{\phi}$ for any $\boldsymbol{a} (\neq \boldsymbol{0})$,where $\boldsymbol{\phi} = (\boldsymbol{\phi}_1', \cdots, \boldsymbol{\phi}_k')'$.

For analysis of nonlinear repeated measurements, recently, Pinheiro and Bates (1999) reviewed statistical analysis (estimation algorithm and analysis of variance) and

* Graduate School of Mathematics, Kyushu University, Hakozaki, Fukuoka 812-8581, Japan.
† Faculty of Mathematics, Kyushu University, Ropponmatsu, Fukuoka 810-8560, Japan. hyakutak@math.kyushu-u.ac.jp

Ogliari and Andrade (2001) consider models in randomized block design. The purpose of this paper is to construct confidence intervals of linear combinations of parameters to know the difference of treatment effects. In Section 2, estimators of the parameters are given by the first order linearization and the approximation for Schéffe type confidence intervals of the specified parameters are constructed. In order to derive the approximated maximum likelihood estimaters, we develop the estimation methods by Vonesh and Carter (1992), see e.g. Chapter 6 of Davidian and Giltinan (1995). A numerical example by using the CO_2 uptake rate data discussed in Potvin, Lechowicz, and Tardif (1990) is given in Section 3.

2. Estimation

In this section, we give the estimators of the parameters and their distributions approximated by the first order linearization. Schéffe type simultaneous confidence intervals on $\boldsymbol{a}'\boldsymbol{\phi}$ are also given.

2.1. Linearization

By the first order Taylor expansion at $\boldsymbol{b}_{ir} = \boldsymbol{0}$, the model $\boldsymbol{f}(\boldsymbol{t};\boldsymbol{\beta}_{ir})$ with $\boldsymbol{\beta}_{ir} = \boldsymbol{\phi}_i + \boldsymbol{b}_{ir}$ in (1.2) is approximated by

$$\boldsymbol{f}(\boldsymbol{t};\boldsymbol{\beta}_{ir}) \approx \boldsymbol{f}(\boldsymbol{t};\boldsymbol{\phi}_i) + Z_{ir}(\boldsymbol{t},\boldsymbol{\phi}_i)\boldsymbol{b}_{ir}, \tag{2.1}$$

where $Z_{ir}(\boldsymbol{t},\boldsymbol{\phi}_i) = \frac{\partial \boldsymbol{f}}{\partial \boldsymbol{\beta}'_{ir}}(\boldsymbol{t};\boldsymbol{\phi}_i)$. Next, by expansion of $\boldsymbol{f}(\boldsymbol{t};\boldsymbol{\phi}_i)$ in (2.1) at $\boldsymbol{\phi}_i = \boldsymbol{\phi}_{i*}$, we have

$$\boldsymbol{f}(\boldsymbol{t};\boldsymbol{\phi}_i) \approx \boldsymbol{g}_i(\boldsymbol{t},\boldsymbol{\phi}_{i*}) + X_i(\boldsymbol{t},\boldsymbol{\phi}_{i*})\boldsymbol{\phi}_i, \tag{2.2}$$

where $X_i(\boldsymbol{t},\boldsymbol{\phi}_{i*}) = \frac{\partial \boldsymbol{f}}{\partial \boldsymbol{\phi}'_i}(\boldsymbol{t};\boldsymbol{\phi}_{i*})$ and $\boldsymbol{g}_i(\boldsymbol{t},\boldsymbol{\phi}_{i*}) = \boldsymbol{f}(\boldsymbol{t};\boldsymbol{\phi}_{i*}) - X_i(\boldsymbol{t},\boldsymbol{\phi}_{i*})\boldsymbol{\phi}_{i*}$. If $Z_{ir}(\boldsymbol{t},\boldsymbol{\phi}_i)$ is approximated by $Z_{ir}(\boldsymbol{t},\boldsymbol{\phi}_{i*})$, then the model (1.2) is approximated by

$$\boldsymbol{y}_{ir} \approx \boldsymbol{g}_i(\boldsymbol{t},\boldsymbol{\phi}_{i*}) + X_i(\boldsymbol{t},\boldsymbol{\phi}_{i*})\boldsymbol{\phi}_i + Z_{ir}(\boldsymbol{t},\boldsymbol{\phi}_{i*})\boldsymbol{b}_{ir} + \boldsymbol{\varepsilon}_{ir}, \tag{2.3}$$

which is the linearization of (1.2). Let $\boldsymbol{y}_i = (\boldsymbol{y}'_{i1},\cdots,\boldsymbol{y}'_{in})'$, then

$$\boldsymbol{y}_i \approx \tilde{\boldsymbol{g}}_i(\boldsymbol{t},\boldsymbol{\phi}_{i*}) + \tilde{X}_i(\boldsymbol{t},\boldsymbol{\phi}_{i*})\boldsymbol{\phi}_i + Z_i(\boldsymbol{t},\boldsymbol{\phi}_{i*})\boldsymbol{b}_i + \boldsymbol{\varepsilon}_i, \tag{2.4}$$

where $\boldsymbol{b}_i = (\boldsymbol{b}'_{i1},\cdots,\boldsymbol{b}'_{in})'$, $\boldsymbol{\varepsilon}_i = (\boldsymbol{\varepsilon}'_{i1},\cdots,\boldsymbol{\varepsilon}'_{in})'$, $\tilde{\boldsymbol{g}}_i(\boldsymbol{t},\boldsymbol{\phi}_*) = \boldsymbol{1}_n \otimes \boldsymbol{g}_i(\boldsymbol{t},\boldsymbol{\phi}_{i*})$, $\tilde{X}_i(\boldsymbol{t},\boldsymbol{\phi}_{i*}) = \boldsymbol{1}_n \otimes X_i(\boldsymbol{t},\boldsymbol{\phi}_{i*})$, $\boldsymbol{1}_n$ is an $n \times 1$ vector of one's, and

$$Z_i(\boldsymbol{t},\boldsymbol{\phi}_{i*}) = \begin{pmatrix} Z_{i1}(\boldsymbol{t},\boldsymbol{\phi}_{i*}) & 0 & \cdots & 0 \\ 0 & Z_{i2}(\boldsymbol{t},\boldsymbol{\phi}_{i*}) & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & Z_{in}(\boldsymbol{t},\boldsymbol{\phi}_{i*}) \end{pmatrix}.$$

Denote the block diagonal matrix like $Z_i(\boldsymbol{t},\boldsymbol{\phi}_{i*})$ as $\mathrm{Diag}(Z_{i1}(\boldsymbol{t},\boldsymbol{\phi}_{i*}),\cdots,Z_{in}(\boldsymbol{t},\boldsymbol{\phi}_{i*}))$ hereafter.

2.2. Confidence Intervals

First of all, we give estimators of unknown parameters, modifying the method developed by of Vonish and Carter (1992). By the linearization (2.4), $\boldsymbol{y}_i$ is distributed as $N(\tilde{g}_i(\boldsymbol{t},\boldsymbol{\phi}_{i*})+\tilde{X}_i(\boldsymbol{t},\boldsymbol{\phi}_{i*})\boldsymbol{\phi}_i, V_i(\sigma_0,\tilde{D},\boldsymbol{t},\boldsymbol{\phi}_{i*}))$, approximately, where $V_i(\sigma_0,\tilde{D},\boldsymbol{t},\boldsymbol{\phi}_{i*}) = Z_i(\boldsymbol{t},\boldsymbol{\phi}_{i*})\ \tilde{D}Z_i(\boldsymbol{t},\boldsymbol{\phi}_{i*})'\ +\sigma_0^2 I_{np}$ and $\tilde{D} = \mathrm{Diag}(D,\cdots,D)$. If σ_0 and D were known, then the approximated log likelihood is given by

$$L(\boldsymbol{\phi},\boldsymbol{b}) = \text{const.} + \frac{1}{\sigma_0^2}\{\boldsymbol{y}-\boldsymbol{g}(\boldsymbol{t},\boldsymbol{\phi}_*) - X\boldsymbol{\phi} - Z\boldsymbol{b}\}'\{\boldsymbol{y}-\boldsymbol{g}(\boldsymbol{t},\boldsymbol{\phi}_*) - X\boldsymbol{\phi} - Z\boldsymbol{b}\} + \boldsymbol{b}'\Psi^{-1}\boldsymbol{b},$$

where $X = \mathrm{Diag}(\tilde{X}_1(\boldsymbol{t},\boldsymbol{\phi}_{1*}),\cdots,\tilde{X}_k(\boldsymbol{t},\boldsymbol{\phi}_{k*}))$, $Z = \mathrm{Diag}(Z_1(\boldsymbol{t},\boldsymbol{\phi}_{1*}),\cdots,Z_k(\boldsymbol{t},\boldsymbol{\phi}_{k*}))$, $\Psi = \mathrm{Diag}(\tilde{D},\cdots,\tilde{D})$, $\boldsymbol{g}(\boldsymbol{t},\boldsymbol{\phi}_*) = (\tilde{g}_1(\boldsymbol{t},\boldsymbol{\phi}_{1*})',\cdots,\tilde{g}_k(\boldsymbol{t},\boldsymbol{\phi}_{k*}))'$, and $\boldsymbol{\phi}_* = (\boldsymbol{\phi}_{1*}',\cdots,\boldsymbol{\phi}_{k*}')'$. Hence the maximum likelihood estimators (MLE) of $\boldsymbol{\phi} = (\boldsymbol{\phi}_1',\cdots,\boldsymbol{\phi}_k')'$ and $\boldsymbol{b} = (\boldsymbol{b}_1',\cdots,\boldsymbol{b}_k')'$ are given by

$$\hat{\boldsymbol{\phi}} = (X'V^{-1}X)^{-1}X'V^{-1}[\boldsymbol{y}-\boldsymbol{g}(\boldsymbol{t},\boldsymbol{\phi}_*)] \tag{2.5}$$

and

$$\hat{\boldsymbol{b}} = \frac{1}{\sigma_0^2}[\Psi^{-1} + \frac{1}{\sigma_0^2}Z(\boldsymbol{t},\boldsymbol{\phi}_*)'Z(\boldsymbol{t},\boldsymbol{\phi}_*)]^{-1}[\boldsymbol{y}-\boldsymbol{g}(\boldsymbol{t},\boldsymbol{\phi}_*) - X\hat{\boldsymbol{\phi}}], \tag{2.6}$$

respectively, where $V = \mathrm{Diag}(V_1(\sigma_0,\tilde{D},\boldsymbol{t},\boldsymbol{\phi}_*),\cdots,\ V_k(\sigma_0,\tilde{D},\boldsymbol{t},\boldsymbol{\phi}_*))$. Applying the matrix identity

$$\frac{1}{\sigma_0^2}[\Psi^{-1} + \frac{1}{\sigma_0^2}Z(\boldsymbol{t},\boldsymbol{\phi}_*)'Z(\boldsymbol{t},\boldsymbol{\phi}_*)]^{-1} = \Psi Z(\boldsymbol{t},\boldsymbol{\phi}_*)V^{-1},$$

see page 78 of Davidian and Giltinan (1995), (2.6) can be written more simply as

$$\hat{\boldsymbol{b}} = \Psi Z(\boldsymbol{t},\boldsymbol{\phi}_*)V^{-1}[\boldsymbol{y}-\boldsymbol{g}(\boldsymbol{t},\boldsymbol{\phi}_*) - X\hat{\boldsymbol{\phi}}]. \tag{2.7}$$

The algorithm for the estimation is follows:
(i) Compute the ordinary least squares estimate $\hat{\boldsymbol{\phi}}_i^{(0)} = (X_i(\boldsymbol{t},\boldsymbol{\phi}_{i*})'X_i(\boldsymbol{t},\boldsymbol{\phi}_*))^{-1}X_i(\boldsymbol{t},\boldsymbol{\phi}_{i*})'$ $(\boldsymbol{y}_i - \boldsymbol{g}_i(\boldsymbol{t},\boldsymbol{\phi}_{i*}))$ for the initial values of $\boldsymbol{\phi}_i$.
(ii) Let $\hat{\boldsymbol{b}}^{(0)} = (Z_0'Z_0)^{-1}Z_0'(\boldsymbol{y}-\boldsymbol{g}_0 - X_0\hat{\boldsymbol{\phi}}^{(0)})$ and

$$\hat{\sigma}_0^2 = \frac{1}{nkp-nkq}(\boldsymbol{y}-X_0\hat{\boldsymbol{\phi}}^{(0)} - Z_0\hat{\boldsymbol{b}}^{(0)})'(\boldsymbol{y}-X_0\hat{\boldsymbol{\phi}}^{(0)} - Z_0\hat{\boldsymbol{b}}^{(0)}),$$

where $Z_0 = Z(\boldsymbol{t},\hat{\boldsymbol{\phi}}^{(0)})$, $\boldsymbol{g}_0 = \boldsymbol{g}(\boldsymbol{t},\hat{\boldsymbol{\phi}}^{(0)})$, and $X_0 = X(\boldsymbol{t},\hat{\boldsymbol{\phi}}^{(0)})$.
(iii) Vonesh and Carter (1992) gave an estimator of D, but their estimtor is not always positive definite. So, we propose the estimator

$$\hat{D} = \begin{cases} \dfrac{1}{nk}\displaystyle\sum_{i=1}^{k}\sum_{r=1}^{n}\hat{b}_{ir}^{(0)}\hat{b}_{ir}^{(0)'} - \dfrac{\hat{\sigma}_0^2}{k}\sum_{i=1}^{k}(Z_{ir_1}(t,\hat{\phi}_i^{(0)})'Z_{ir_1}(t,\hat{\phi}_i^{(0)}))^{-1} & (\text{if } \ell_q > \hat{\sigma}_0^2) \\ \dfrac{1}{nk}\displaystyle\sum_{i=1}^{k}\sum_{r=1}^{n}\hat{b}_{ir}^{(0)}\hat{b}_{ir}^{(0)'} - \dfrac{\ell_q - c}{k}\sum_{i=1}^{k}(Z_{ir_1}(t,\hat{\phi}_i^{(0)})'Z_{ir_1}(t,\hat{\phi}_i^{(0)}))^{-1} & (\text{if } \ell_q \le \hat{\sigma}_0^2), \end{cases}$$

where ℓ_q is the minimum root of the equation

$$|\frac{1}{nk}\sum_{i=1}^{k}\sum_{r=1}^{n}\hat{b}_{ir}^{(0)}\hat{b}_{ir}^{(0)'} - \frac{\ell}{k}\sum_{i=1}^{k}(Z_{ir_1}(t,\hat{\phi}_i^{(0)})'Z_{ir_1}(t,\hat{\phi}_i^{(0)}))^{-1}| = 0,$$

$r_1 \in \{1, \cdots, n\}$, and c is a small number so that $\hat{D}$ is positive definite. The choise of c is discussed later.

(iv) Based on (2.5), the MLE of ϕ is derived by iteration

$$\hat{\phi}^{(l)} = (X^{(l-1)'}V^{(l-1)^{-1}}X^{(l-1)})^{-1}X^{(l-1')}V^{(l-1)^{-1}}[y - g(t, \phi^{(l-1)})], \tag{2.8}$$

where $X^{(l-1)} = X(t, \hat{\phi}^{(l-1)})$ and $V^{(l-1)} = V(\hat{\sigma}_0, \hat{\tilde{D}}, t, \hat{\phi}^{(l-1)})$. By (2.7) and (2.8),

$$\hat{b} = \hat{\Psi}Z(t, \hat{\phi})'V(\hat{\sigma}_0, \hat{\tilde{D}}, t, \hat{\phi})^{-1}[y - g(t, \hat{\phi}) - X(t, \hat{\phi}]\hat{\phi}).$$

We choose the value of ϕ_* in (i) by looking at data as described in Vonesh and Carter (1992). On the estimation of D in (iii), if we extend Vonesh and Carater (1992) straightforward, $(\ell_q - c)/k$ in $\hat{D}$ is ℓ_q/k, that is $c = 0$ in our estimator.

By linearization, the distribution of $\hat{\phi}$ is approximated by

$$N(\phi, \{X(t, \phi_*)'V(\sigma_0, \tilde{D}, t, \phi_*)^{-1}X(t, \phi_*)\}^{-1}). \tag{2.9}$$

Hence $(\hat{\phi} - \phi)'X(t, \phi_*)'V(\sigma_0, \tilde{D}, t, \phi_*)^{-1}X(t, \phi_*)(\hat{\phi} - \phi)$ has the chi-square distribution with qk degrees of freedom (χ^2_{qk}), approximately. If we are interested in the comparison of specified paremeters $\phi_{ii'}$, i'th elements of ϕ_i $(i = 1, \cdots, k)$, then the coresponding marginal distribution is also normal. Let $\xi = (\phi_{1i'}, \cdots, \phi_{ki'})'$ and $\hat{\xi} = (\hat{\phi}_{1i'}, \cdots, \hat{\phi}_{ki'})'$, then $(\hat{\xi} - \xi)'\Sigma_0^{-1}(\hat{\xi} - \xi)$ has χ^2_k, approximately, where Σ_0 is the covariance matrix of the corresponding elements of $\{X(t, \phi_*)'V(\sigma_0, \tilde{D}, t, \phi_*)^{-1}X(t, \phi_*)\}^{-1}$ in (2.9). Hence the approximated $100(1 - \alpha)\%$ simultaneous confidence intervals are given by

$$a'\xi \in a'\hat{\xi} \pm \sqrt{\chi^2_k(\alpha)a'\Sigma_0 a}, \tag{2.10}$$

where $\chi^2_k(\alpha)$ is the upper $100(1 - \alpha)\%$ point of χ^2_k and a $(\neq 0)$ is any k dimensional vector. For practical application, we use the estimators $\hat{\phi}, \hat{\sigma}_0, \hat{D}$ instead of ϕ_*, σ_0, D.

3. Simulation and Numerical Example

In this section, we give a numerical example by using data from Potvin, Lechowicz, and Tardif (1990), or see Pinheiro and Bates (1999). The data measured the uptake rate ($\mu mol/m^2 l$) of CO_2 of different types of plants, Echinochloa crus-galli, at some concentrations of ambient CO_2. The number of plants are 6 from Quebec and 6 from Mississsippi, and 3 plants of Quebec and 3 plants of Mississsippi are chilled and remaining plants are nonchilled. The uptake experiment is two-way layout, type of plant (Quebec or Mississippi) and treatment (chilled or nonchilled). We use the notations "QN" for Quebec and nonchilled, "QC" for Quebec and chilled, "MN" for Mississippi and nonchilled, and "MC" for Mississippi and chilled. In this experiment, Potvin, Lechowicz, and Tardif (1990) assume the model

$$y_{ir,j} = \beta_{ir1}\{1 - \exp[-e^{\beta_{ir2}}(t_j - \beta_{ir3})]\} + \varepsilon_{ir,j}, \tag{3.1}$$

where β_{ir1} is the asymptotic uptake rate parameter, β_{ir2} is the uptake growth rate parameter, and β_{ir3} is the maximum ambient CO_2 concentration at which no uptake is verified for the ith plant. These parameters are written by $(\beta_{ir1}, \beta_{ir2}, \beta_{ir3}) = (\phi_{i1} + b_{ir1}, \phi_{i2} + b_{ir2}, \phi_{i3} + b_{ir3})$ as assumed in Section 1. The concentrations of ambient CO_2 level (t_j) are 95, 175, 250, 350, 500, 675, 1000 ($\mu l/l$), that is $p = 7$. Pinheiro and Bates (1999) gave estimated random effects under $\phi_{11} = \cdots = \phi_{41}, \phi_{12} = \cdots = \phi_{42}, \phi_{13} = \cdots = \phi_{43}$. They suggest that the asymptotic uptake rate parameter and the maximum ambient CO_2 concentration are significant and that the uptake growth rate parameter is not significant by plotting the estimated random effects. They also suggests that type of plant and treatment have a stronger influence on the asymptotic uptake rate parameter than on the maximum ambient CO_2 concentration by using the anova method in S-PLUS. But they do not compare the influence on the parameters by type and treatment. Our interest is to compare the asymptotic uptake rate parameters. We use $\phi_{i*} = (30, \log(0.01), 50)'$ for numerical computation, the value is recommemded in Pinheiro and Bates (1999).

3.1. Simulation

We examine the effect of the choice of c in the proposed estimator $\hat{D}$ by simulation. In the simulation, we consider similar situation to CO_2 uptake rate experiment, hence we choose the model (3.1), $k = 4$, and the observed points are the same as above. The parameters are as follows:

$$\begin{array}{lll} \phi_{11} = 42 & \phi_{12} = -4.5 & \phi_{13} = 50 \\ \phi_{21} = 39 & \phi_{22} = -4.7 & \phi_{23} = 50 \\ \phi_{31} = 31 & \phi_{32} = -4.6 & \phi_{33} = 48 \\ \phi_{41} = 18 & \phi_{42} = -4.6 & \phi_{43} = 16, \end{array}$$

$\sigma_0 = 1$, and

$$D = \begin{pmatrix} 1 & -0.02 & 1 \\ -0.02 & 0.004 & 0.16 \\ 1 & 0.16 & 12 \end{pmatrix}.$$

The sample sizes (n) from each population is 12. Under these situation, 200 estimates $(\hat{D})$ are computed and the average $\bar{\hat{D}}$ of 200 $\hat{D}$ are also computed. We examine the values of $\mathrm{tr}(D\bar{\hat{D}}^{-1} - I)$ for some values of c. The results are in Table 1.

Table 1. Effect by Choice of c

c	0.0001	0.001	0.01	0.05	0.10
$\mathrm{tr}(D\bar{\hat{D}}^{-1}) - 3$	-1.26	-1.31	-1.28	-1.30	-1.54

From this Table, there is not much difference by choice of c. We use $c = 0.01$ for the numerical example in the next subsection. We also examine the accuracy of approximation for the distribution of $(\hat{\phi} - \phi)'X(t, \hat{\phi})'V(\hat{\sigma}_0, \bar{\hat{D}}, t, \hat{\phi})^{-1}X(t, \hat{\phi})(\hat{\phi} - \phi)$. Under the same situation as above, 2000 statistics are computed, then the upper 5% point is 22.8, which is close to $\chi^2_{12}(0.05) = 21.03$. In this simulation, if we use the straightforward extension of Vonish and Carter (1992), computation of the estimates does not work well sometimes. In the next numerical example, it would be possible to compute the statistics, but we use the proposed procedure.

3.2. Numerical Example

We give a numerical example for constructing the simultaneous confidence intervals of the asymptotic uptake rate parameters ϕ_{i1}'s in the model (3.1) for the CO_2 uptake rate data from Potvin, Lechowicz, and Tardif (1990). The estimates computed by the method proposed in Section 2 are

i	1 (QN)	2 (QC)	3 (MN)	4 (MC)
$\hat{\phi}_{i1}$	41.8	38.9	31.3	17.8
$\hat{\phi}_{i2}$	-4.5	-4.7	-4.6	-4.6
$\hat{\phi}_{i3}$	52.9	50.4	47.9	15.5

$\hat{\sigma}_0 = 1.81$, and

$$\hat{D} = \begin{pmatrix} 6.08 & -0.204 & -1.21 \\ -0.204 & 0.056 & 2.2 \\ -1.21 & 2.2 & 96.5 \end{pmatrix}.$$

The 95% simultaneous confidence intervals for some values of $\boldsymbol{a}$ are in Table 2. For example, the difference between QN and QC can be seen by $\boldsymbol{a} = (1, -1, 0, 0)'$, the difference between Quebec and Mississipi can be seen by $\boldsymbol{a} = (1, 1, -1, -1)'$, and so on.

Table 2. Simultaneous Confidence Intervals

a'	Confidence Interval
(1,-1,0,0)	[-8.74, 14.54]
(0,0,1,-1)	[1.83, 25.13]
(1,0,-1,0)	[-1.19, 22.07]
(0,1,0,-1)	[9.35, 32.74]
(1,-1,1,-1)	[-0.12, 32.80]
(1,1,-1,-1)	[14.98, 47.98]

From this Table, we see that the difference of $\phi_{11} + \phi_{21}$ and $\phi_{31} + \phi_{41}$ (Quebec and Mississippi) is significant, but $\phi_{11} + \phi_{31}$ and $\phi_{21} + \phi_{41}$ (nonchilled and chilled) is not significant. Hence it would be seen that the asymptotic uptake rate is effected by the type rather than the treatment.

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