Hiroshima Math. J.
37 (2007), 111–117

Confidence regions of parameters in a nonlinear repeated measurement model with mixed effects

Dedicated to Professor Y. Fujikoshi on his retirement from Hiroshima University

Yuko Baba, Hirofumi Nishimaru and Hiroto Hyakutake

(Received March 8, 2006)
(Revised September 27, 2006)

Abstract. There are several nonlinear models for analyzing repeated measurements. The mean response for an individual depends on the regression parameter specific to that individual. One of the simple form is the sum of a vector of fixed parameters and a vector of random effect. In this paper, we give a confidence region of the fixed parameters approximately.

1. Introduction

Let $\boldsymbol{y}_i = (y_{i1}, \dots, y_{ip})'$ be a p dimensional observation of the ith individual $(i = 1, \dots, n)$, in which the element y_{ij} is measured at point t_j. $\boldsymbol{y}_i$ is called the repeated measurement data. For each element y_{ij}, we assume

$$y_{ij} = f(t_j; \boldsymbol{\beta}_i) + \varepsilon_{ij}, \tag{1.1}$$

where f is a known (nonlinear) function, ε_{ij} is the error, and $\boldsymbol{\beta}_i = (\beta_{i1}, \dots, \beta_{iq})'$ is unknown parameter $(q < p)$. For example, such data arise in pharmacokinetics, growth processes, and so on; see Davidian and Giltinan [1] or Vonesh and Chinchilli [7]. Let $\boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\beta}_i) = (f(t_1; \boldsymbol{\beta}_i), \dots, f(t_p; \boldsymbol{\beta}_i))'$, then

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

where $\boldsymbol{\varepsilon}_i = (\varepsilon_{i1}, \dots, \varepsilon_{ip})'$ and $\boldsymbol{t} = (t_1, \dots, t_p)'$. In the model, $\boldsymbol{\beta}_i = \boldsymbol{\phi} + \boldsymbol{b}_i$ is assumed, where $\boldsymbol{\phi} = (\phi_1, \dots, \phi_q)'$ is the fixed parameter and $\boldsymbol{b}_i = (b_{i1}, \dots, b_{iq})'$ is the random effect. We assume that $\boldsymbol{\varepsilon}_i$'s are independent and have multinormal distribution with mean $\mathbf{0}$ and covariance matrix $\sigma^2 I_p$, that is $N_p(\mathbf{0}, \sigma^2 I_p)$, that $\boldsymbol{b}_i$'s are independent and have $N_q(\mathbf{0}, \Psi)$, and that $\boldsymbol{\varepsilon}_i$ and $\boldsymbol{b}_i$ are independent. Then we wish to construct a confidence region for $\boldsymbol{\phi}$.

2000 *Mathematics Subject Classification*. 62F25, 62J99.
Key words and phrases. Confidence region, nonlinear model, repeated measurements.

For analysis of nonlinear repeated measurements, Pinheiro and Bates [4] reviewed statistical analysis, Vonesh [5] gave an estimation algorithm and a confidence interval of a parameter, and Nagahisa and Hyakutake [3] gave simultaneous confidence intervals of the parameters. But the confidence interval by Vonesh [5] is only for one parameter of $\boldsymbol{\phi}$ and Nagahisa and Hyakutake [3] gave confidence intervals based on an asymptotic distribution. In Section 2, we give an approximate confidence region for $\boldsymbol{\phi}$ by the first order linearization. Vonesh [5] examined the efficiency of four types of estimators by simulation, in which no one estimator is universally better or worth than the others. We use the estimated generalized least squares (EGLS). In Section 3, the accuracy of approximation is examined by simulation.

2. Confidence region

By the first order Taylor expansion at $\boldsymbol{\beta}_i = \boldsymbol{\phi}$, the nonlinear function $\boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\beta}_i)$ is approximated by

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

where $Z(\boldsymbol{\phi}) = \partial \boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\beta}_i)/\partial \boldsymbol{\beta}_i'|_{\boldsymbol{\beta}_i = \boldsymbol{\phi}}$. Since the model (1.2) can be approximated by

$$\boldsymbol{y}_i \approx \boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\phi}) + Z(\boldsymbol{\phi})\boldsymbol{b}_i + \boldsymbol{\varepsilon}_i, \tag{2.2}$$

the distribution of $\boldsymbol{y}_i$ is $N_p(\boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\phi}), W^{-1})$ approximately, where

$$W^{-1} = W^{-1}(\Psi, \sigma^2) = Z\Psi Z' + \sigma^2 I_p. \tag{2.3}$$

Given model (2.2), Vonesh and Carter [6] and Vonesh [5] described EGLS procedure:

Stage 1: Obtain the ordinary least square (OLS) estimator $\tilde{\boldsymbol{\phi}}$.

Stage 2: Set $\tilde{Z} = Z(\tilde{\boldsymbol{\phi}})$ and treat as a known matrix. Let $\tilde{\boldsymbol{e}}_i = \boldsymbol{y}_i - \boldsymbol{f}(\boldsymbol{t}; \tilde{\boldsymbol{\phi}})$, $\tilde{\boldsymbol{b}}_i = (\tilde{Z}'\tilde{Z})^{-1}\tilde{Z}'\tilde{\boldsymbol{e}}_i$, and $\tilde{s}_i^2 = \tilde{\boldsymbol{e}}_i'\{I_p - \tilde{Z}(\tilde{Z}'\tilde{Z})^{-1}\tilde{Z}'\}\tilde{\boldsymbol{e}}_i/(p-q)$.

Stage 3: Obtain estimates of σ^2 and Ψ as

$$\hat{\sigma}^2 = \sum_{i=1}^{n} \tilde{s}_i^2/n \qquad \text{and} \qquad \hat{\Psi} = \begin{cases} S_{\tilde{b}} - \hat{\sigma}^2(\tilde{Z}'\tilde{Z})^{-1} & (\hat{\lambda} > \hat{\sigma}^2) \\ S_{\tilde{b}} - \hat{\lambda}(\tilde{Z}'\tilde{Z})^{-1} & (\hat{\lambda} \leq \hat{\sigma}^2) \end{cases}, \tag{2.4}$$

where $S_{\tilde{b}} = \sum_{i=1}^{n} \tilde{\boldsymbol{b}}_i\tilde{\boldsymbol{b}}_i'/n$ and $\hat{\lambda}$ is the minimum root of $|S_{\tilde{b}} - \lambda(\tilde{Z}'\tilde{Z})^{-1}| = 0$.

Stage 4: Obtain the EGLS estimator $\hat{\boldsymbol{\phi}}$ by minimizing

$$\sum_{i=1}^{n} \{\boldsymbol{y}_i - \boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\phi})\}'\hat{W}\{\boldsymbol{y}_i - \boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\phi})\}, \tag{2.5}$$

where $\hat{W} = (\tilde{Z}\hat{\Psi}\tilde{Z}' + \hat{\sigma}^2 I_p)^{-1}$.

If Ψ and σ^2 were known, then the generalized least squares (GLS) estimator is obtained by minimizing

$$\sum_{i=1}^{n}\{\boldsymbol{y}_i - \boldsymbol{f}(\boldsymbol{t};\boldsymbol{\phi})\}' W \{\boldsymbol{y}_i - \boldsymbol{f}(\boldsymbol{t};\boldsymbol{\phi})\}, \tag{2.6}$$

and its covariance matrix is approximated by $\Omega = (nZ'WZ)^{-1}$. So, $\hat{\Omega} = (n\hat{Z}'\hat{W}\hat{Z})^{-1}$ is used as the covariance matrix of the EGLS estimator $\hat{\boldsymbol{\phi}}$, where $\hat{Z} = Z(\hat{\boldsymbol{\phi}})$. But Vonesh [5] recommended to use the following robust covariance matrix estimate

$$\hat{\Omega}_R = \hat{\Omega}\hat{Z}'\hat{W}\sum_{i=1}^{n}\{\boldsymbol{y}_i - \boldsymbol{f}(\boldsymbol{t};\hat{\boldsymbol{\phi}})\}\{\boldsymbol{y}_i - \boldsymbol{f}(\boldsymbol{t};\hat{\boldsymbol{\phi}})\}'\hat{W}\hat{Z}\hat{\Omega}. \tag{2.7}$$

Vonesh [5] gave a confidence interval for ϕ_l $(l = 1, \dots, q)$ by using a Student's t approximation with $n - q$ degrees of freedom (df). This is extended to a $100(1-\alpha)\%$ confidence region for $\boldsymbol{\phi}$ as

$$(\hat{\boldsymbol{\phi}} - \boldsymbol{\phi})'\hat{\Omega}_R^{-1}(\hat{\boldsymbol{\phi}} - \boldsymbol{\phi}) \le \frac{q(n-q)}{n-2q+1}F_{q,n-2q+1}(\alpha), \tag{2.8}$$

where $F_{r_1,r_2}(\alpha)$ is an upper α point of F-distribution with (r_1, r_2) df.

Here we wish to give another confidence region. Let $\boldsymbol{\xi}_i = Z(\boldsymbol{\phi})\boldsymbol{b}_i + \boldsymbol{\varepsilon}_i$, then the model (2.2) is written by

$$\boldsymbol{y}_i \approx \boldsymbol{f} + \xi_i, \tag{2.9}$$

where $\boldsymbol{f} = \boldsymbol{f}(\boldsymbol{t};\boldsymbol{\phi})$. Hyakutake [2] derived simultaneous confidence intervals for pairwise comparisons under the model (2.9), in which the OLS esimators were used. By the first order Taylor expansion at $\hat{\boldsymbol{\phi}} = \boldsymbol{\phi}$, we have

$$\hat{\boldsymbol{f}} = \boldsymbol{f}(\boldsymbol{t};\hat{\boldsymbol{\phi}}) \approx \boldsymbol{f}(\boldsymbol{t};\boldsymbol{\phi}) + Z(\hat{\boldsymbol{\phi}} - \boldsymbol{\phi}). \tag{2.10}$$

Since the EGLS estimator is obtained by minimizing (2.5), $Z'W\sum_{i=1}^{n}(\boldsymbol{y}_i - \hat{\boldsymbol{f}}) \approx \mathbf{0}$. Hence

$$\begin{aligned}\mathbf{0} &\approx Z'W\sum\nolimits_{i=1}^{n}(\boldsymbol{y}_i - \hat{\boldsymbol{f}})\\ &\approx Z'W\sum\nolimits_{i=1}^{n}\{\boldsymbol{y}_i - \boldsymbol{f} - Z(\hat{\boldsymbol{\phi}} - \boldsymbol{\phi})\}\\ &\approx Z'W\sum\nolimits_{i=1}^{n}\xi_i - nZ'WZ(\hat{\boldsymbol{\phi}} - \boldsymbol{\phi})\end{aligned} \tag{2.11}$$

Hence $Z'WZ(\hat{\boldsymbol{\phi}} - \boldsymbol{\phi}) \approx Z'W\bar{\xi}$, where $\bar{\xi} = \sum_{i=1}^{n}\xi_i/n$. Since ξ_i is approximately distributed as $N_p(\mathbf{0}, W^{-1})$, the distribution of $\hat{\boldsymbol{\phi}} - \boldsymbol{\phi}$ is approximately

$N_q(\mathbf{0}, (Z'WZ)^{-1}/n)$. We assumed that $\boldsymbol{\varepsilon}_i$ and $\boldsymbol{b}_i$ have normal distribution. Even if these are not normal, $\hat{\boldsymbol{\phi}} - \boldsymbol{\phi}$ is approximately distributed as normal under the large sample. By the same method of Hyakutake [2] and (2.10), we have

$$
\begin{aligned}
V &= \sum\nolimits_{i=1}^{n} (\boldsymbol{y}_i - \hat{\boldsymbol{f}})(\boldsymbol{y}_i - \hat{\boldsymbol{f}})' \\
&\approx \sum\nolimits_{i=1}^{n} \{\boldsymbol{y}_i - \boldsymbol{f} - Z(\hat{\boldsymbol{\phi}} - \boldsymbol{\phi})\}\{\boldsymbol{y}_i - \boldsymbol{f} - Z(\hat{\boldsymbol{\phi}} - \boldsymbol{\phi})\}' \\
&\approx \sum\nolimits_{i=1}^{n} \{(\xi_i - \bar{\xi}) + \bar{\xi} - Z(\hat{\boldsymbol{\phi}} - \boldsymbol{\phi})\}\{(\xi_i - \bar{\xi}) + \bar{\xi} - Z(\hat{\boldsymbol{\phi}} - \boldsymbol{\phi})\}' \\
&= \sum\nolimits_{i=1}^{n} (\xi_i - \bar{\xi})(\xi_i - \bar{\xi})' + n\{\bar{\xi} - Z(\hat{\boldsymbol{\phi}} - \boldsymbol{\phi})\}\{\bar{\xi} - Z(\hat{\boldsymbol{\phi}} - \boldsymbol{\phi})\}'.
\end{aligned}
$$

Since $Z'WZ(\hat{\boldsymbol{\phi}} - \boldsymbol{\phi}) - Z'W\bar{\xi} \approx \mathbf{0}$ by (2.11), it is easy to see that

$$
Z'WVWZ \approx Z'W \left\{ \sum_{i=1}^{n} (\xi_i - \bar{\xi})(\xi_i - \bar{\xi})' \right\} WZ. \tag{2.12}
$$

Because ξ_i $(i = 1, \ldots, n)$ are independently and identically distributed as the multinormal, the statistic (2.12) has the Wishart distribution with the covariance matrix $Z'WZ$ and $n-1$ df, that is $W_q(Z'WZ, n-1)$, approximately. Then the approximated distribution of $\Omega_R = \Omega Z'WVWZ\Omega$ is $W_q\{(Z'WZ)^{-1}/n^2, n-1\}$. Hence the distribution of the robust covariance matrix estimate $\hat{\Omega}_R$ in (2.7) would be approximated by $W_q\{(Z'WZ)^{-1}/n^2, n-1\}$. Since $(\hat{\boldsymbol{\phi}} - \boldsymbol{\phi})/\sqrt{n}$ has $N_q(\mathbf{0}, (Z'WZ)^{-1}/n^2)$ approximately, the statistic

$$
\frac{n-q}{qn} (\hat{\boldsymbol{\phi}} - \boldsymbol{\phi})' \hat{\Omega}_R^{-1} (\hat{\boldsymbol{\phi}} - \boldsymbol{\phi}) \tag{2.13}
$$

has F-distribution with $(q, n-q)$ df approximately. Thus we have an approximated $100(1-\alpha)\%$ confidence region for $\boldsymbol{\phi}$ as

$$
(\hat{\boldsymbol{\phi}} - \boldsymbol{\phi})' \hat{\Omega}_R^{-1} (\hat{\boldsymbol{\phi}} - \boldsymbol{\phi}) \leq \frac{qn}{n-q} F_{q,n-q}(\alpha). \tag{2.14}
$$

3. Simulation

Two approximated confidence regions (2.8) and (2.14) are given in the previous section. In this section, we examine the accuracy of approximation by simulation. Two nonlinear models

$$
f_{pharm}(t; \boldsymbol{\beta}_i) = \beta_{i1} t \exp(-\beta_{i2} t) \tag{3.1}
$$

Table 1. Parameters and variance

Model	ϕ_1	ϕ_2	σ^2
f_{pharm}	1.0	0.5	0.01, 0.0001
f_{logit}	2.0	1.5	0.001, 0.00001

and

$$f_{logit}(t;\boldsymbol{\beta}_i) = \{1 + \beta_{i1}\exp(-\beta_{i2}t)\}^{-1}. \tag{3.2}$$

are used in the simulation, where $\beta_{il} = \phi_l + b_{il}$ $(l = 1, 2)$. The model (3.1) and (3.2) are the special cases of a pharmacokinetic model and a logistic model, respectively. We choose the parameters and the variance of ε_{ij}, which are generated from $N(0, \sigma^2)$, for each model as in Table 1.

The observed points are $t = 1, 2, 3, 4, 5$ $(p = 5)$ for model (3.1) and $t = 1, 2, 3, 4$ $(p = 4)$ for model (3.2). The sample sizes from the population are $n = 15, 25, 30$. The random effects $\boldsymbol{b}_i = (b_{i1}, b_{i2})'$ are generated from $N_2(\mathbf{0}, \Psi_l)$ $(l = 1, 2, 3, 4)$. The covariance matrices of the random effects are Ψ_1 and Ψ_2 for model (3.1) and Ψ_3 and Ψ_4 for model (3.2), where

$$\Psi_1 = \begin{pmatrix} 0.002 & 0.0007 \\ 0.0007 & 0.001 \end{pmatrix}, \qquad \Psi_2 = \begin{pmatrix} 0.004 & 0.0007 \\ 0.0007 & 0.002 \end{pmatrix}$$

$$\Psi_3 = \begin{pmatrix} 0.0025 & 0.0005 \\ 0.0005 & 0.0025 \end{pmatrix}, \qquad \Psi_4 = \begin{pmatrix} 0.0049 & 0.0005 \\ 0.0005 & 0.0049 \end{pmatrix}.$$

If the values of the variances are larger than the values chosen in the above, then the variation by the error is sometimes larger than that by the model. For these values and $\alpha = 0.05$, 1,000 confidence regions are constructed in each of (2.8) and (2.14). The proportion, that the confidence regions include true values of ϕ_1 and ϕ_2, is calculated. The results are in Tables 2 and 3.

Table 2. Accuracy of approximation in model f_{pharm}

Conf.	σ^2 Region	0.01 (2.8)	(2.14)	0.0001 (2.8)	(2.14)
Ψ_1	$n = 15$	0.932	0.940	0.944	0.950
	$n = 25$	0.944	0.950	0.951	0.956
	$n = 30$	0.948	0.954	0.925	0.932
Ψ_2	$n = 15$	0.931	0.941	0.930	0.937
	$n = 25$	0.924	0.930	0.900	0.906
	$n = 30$	0.948	0.951	0.913	0.914

Table 3. Accuracy of approximation in model f_{logit}

Conf.	σ^2 Region	0.001 (2.8)	(2.14)	0.00001 (2.8)	(2.14)
Ψ_3	$n = 15$	0.947	0.951	0.944	0.947
	$n = 25$	0.944	0.947	0.937	0.942
	$n = 30$	0.948	0.951	0.931	0.936
Ψ_4	$n = 15$	0.935	0.940	0.923	0.929
	$n = 25$	0.949	0.957	0.924	0.933
	$n = 30$	0.929	0.934	0.921	0.925

From Tables 2 and 3, the approximation by (2.14) is somewhat better than that by (2.8) in both models. So, we recommend to use (2.14). When σ^2 is small and Ψ is large, the approximation is not good. For interval estimation of the component ϕ_l, Vonesh [5] used t approximation with $n - q$ df, but it would be better to use t approximation with $n - 1$ df.

References

[1] D. Davidian and D. M. Giltinan, Nonlinear Models for Repeated Measurement Data, Chapman & Hall/CRC, 1995.
[2] H. Hyakutake, Multiple comparisons in nonlinear repeated measurements, Biometrical J., **45** (2003), 772–780.
[3] T. Nagahisa and H. Hyakutake, Simultaneous confidence intervals for parameters in nonlinear models of repeated measurements, Bull. Informatics and Cybernetics, **35** (2003), 19–25.
[4] J. C. Pinheiro and D. M. Bates, Mixed Effects Methods and Classes for S and S-PLUS Version 3.0, (http://cm.bell-labs.com/cm/ms/departments/sia/project/nlme).
[5] E. F. Vonesh, Non-linear models for the analysis of longitudinal data, Statist. Medicine, **11** (1992), 1929–1954.
[6] E. F. Vonesh and R. L. Carter, Mixed-effects nonlinear regression for unbalanced repeated measures, Biometrics, **48** (1992), 1–17.
[7] E. F. Vonesh and V. M. Chinchilli, Linear and Nonlinear Models for the Analysis of Repeated Measurements, Dekker, 1997.

Yuko Baba
Biostatistics Department
SHIONOGI CO., LTD.
5-12-4, *Sagisu, Fukushima-ku*
Osaka 553-0002, *Japan*
E-mail: yuuko.baba@shionogi.co.jp

Hirofumi Nishimaru
Graduate School of Mathematics
Kyushu University
4-2-1 *Ropponmatsu, Chuo-ku*
Fukuoka 810-8560, *Japan*

Hiroto Hyakutake
Faculty of Mathematics
Kyushu University
4-2-1 *Ropponmatsu, Chuo-ku*
Fukuoka 810-8560, *Japan*
E-mail: hyakutak@math.kyushu-u.ac.jp