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PAIRWISE COMPARISONS FOR PARALLEL PROFILE MODELS WITH MIXED EFFECTS

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ABSTRACT. There are several linear and nonlinear models for analyzing repeated measurements. The mean response for an individual depends on the regression parameters specific to that individual. One of the simple forms is the sum of vectors of fixed parameters and random effects. When the models with mixed effects for several groups are parallel, pairwise comparisons of level differences are considered. For the comparisons, approximate simultaneous confidence intervals are given.

1. Introduction

Let $\boldsymbol{y}_{ij} = (y_{ij,1}, \dots, y_{ij,p})'$ be a p dimensional observation of the jth individual from the ith population ($i = 1, \dots, k$; $j = 1, \dots, n$), in which $y_{ij,r}$ is measured at point t_r. For each element $y_{ij,r}$, we assume

$$y_{ij,r} = \gamma_i + f(t_r; \boldsymbol{\beta}_{ij}) + \varepsilon_{ij,r},$$

where γ_i is a level difference parameter such that $\sum_i \gamma_i = 0$, f is a known function, $\varepsilon_{ij,r}$ is the error, and $\boldsymbol{\beta}_{ij}$ is a q dimensional vector of unknown parameter ($q < p$). For example, such data arise in pharmacokinetics, growth processes, and so on. Let $\boldsymbol{f} = \boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\beta}_{ij}) = \big(f(t_1; \boldsymbol{\beta}_{ij}), \dots, f(t_p; \boldsymbol{\beta}_{ij})\big)'$, then the model can be written as

$$\boldsymbol{y}_{ij} = \gamma_i \mathbf{1}_p + \boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\beta}_{ij}) + \boldsymbol{\varepsilon}_{ij}, \tag{1}$$

where $\mathbf{1}_p$ is a p vector of ones, $\boldsymbol{t} = (t_1, \dots, t_p)'$, and $\boldsymbol{\varepsilon}_{ij} = (\varepsilon_{ij,1}, \dots, \varepsilon_{ij,p})'$ is independently distributed as the p-variate normal with mean $\mathbf{0}$ and covariance matrix $\sigma^2 I_p$, say $N_p(\mathbf{0}, \sigma^2 I_p)$. In this model, it is assumed that $\boldsymbol{\beta}_{ij} = \boldsymbol{\phi} + \boldsymbol{b}_{ij}$, where $\boldsymbol{\phi}$ is the fixed parameter and $\boldsymbol{b}_{ij}$ is the random effect, which is independent of $\boldsymbol{\varepsilon}$ and is distributed as $N_q(\mathbf{0}, \Psi)$. When $\boldsymbol{f} = (\mu_{i1}, \dots, \mu_{ip})'$, the model has

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no random effect and the k models are parallel in the sense of Srivastava [7], in which the problem of testing "Parallelism" and "Level Differences" are considered. So, the model (1) can be called a "parallel profile model". We wish to construct confidence intervals of the level differences $\gamma_i - \gamma_{i'}$, under the model (1). Under Srivastava's parallel profile model, Hyakutake and Fujimaru [5] considered multiple directional decisions with a control.

Inferences of parameters in nonlinear models for repeated measurements are summarized in Davidian and Giltinan [2]. Vonesh and Carter [9] gave an estimation algorithm and Baba et al. [1] gave approximate confidence regions for $\boldsymbol{\phi}$. In this paper, we give approximate simultaneous confidence intervals for $\gamma_i - \gamma_{i'}$ $(i < i')$ based on Tukey's method (see, e.g., Hsu [4]). In Section 2, an estimation algorithm based on Vonesh and Carter [9] and approximate confidence intervals for pairwise comparisons of the level differences are given. Vonesh [8] examined the efficiency of four types of estimators of $\boldsymbol{\phi}$ by simulation, in which no one estimator is universally better or worse than the others. We use the estimated generalized least squares (EGLS). In Section 3, we examine the accuracy of approximation by simulation and give an example.

2. Simultaneous confidence intervals

By the first-order Taylor expansion at $\boldsymbol{\beta}_{ij} = \boldsymbol{\phi}$, the model (1) can be approximated by

$$\boldsymbol{y}_{ij} \approx \gamma_i \mathbf{1}_p + \boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\phi}) + Z(\boldsymbol{\phi})\boldsymbol{b}_{ij} + \boldsymbol{\varepsilon}_{ij}, \tag{2}$$

where $Z(\boldsymbol{\phi}) = \partial \boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\beta}_{ij})/\partial \boldsymbol{\beta}'_{ij}|_{\boldsymbol{\beta}_{ij}=\boldsymbol{\phi}}$. Then the distribution of $\boldsymbol{y}_{ij}$ is $N_p\big(\gamma_i \mathbf{1}_p + \boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\phi}), \Sigma\big)$ approximately, where $\Sigma = \Sigma(\Psi, \sigma^2) = Z(\boldsymbol{\phi})\Psi Z(\boldsymbol{\phi})' + \sigma^2 I_p$. Under this approximation, it is easy to see that the maximum likelihood estimator of γ_i is $\mathbf{1}'_p \Sigma^{-1}(\bar{\boldsymbol{y}}_i - \bar{\boldsymbol{y}}_\cdot)/\mathbf{1}'_p \Sigma^{-1} \mathbf{1}_p$, when Σ is known, where $\bar{\boldsymbol{y}}_i = \sum_j \boldsymbol{y}_{ij}/n$ and $\bar{\boldsymbol{y}}_\cdot = \sum_{i,j} \boldsymbol{y}_{ij}/kn$. Under the approximation by the first-order Taylor expansion, Vonesh and Carter [9] described the EGLS procedure for estimation of $\boldsymbol{\phi}$. We extend this procedure to the approximated model (2) as follows:

i) Compute

$$\tilde{\tilde{\gamma}}_i = \mathbf{1}'_p V^{-1}(\bar{\boldsymbol{y}}_i - \bar{\boldsymbol{y}}_\cdot)/\mathbf{1}'_p V^{-1} \mathbf{1}_p, \quad \text{where} \quad V = \sum_{i,j} (\boldsymbol{y}_{ij} - \bar{\boldsymbol{y}}_i)(\boldsymbol{y}_{ij} - \bar{\boldsymbol{y}}_i)'.$$

ii) Obtain the ordinary least square estimator $\tilde{\boldsymbol{\phi}}$ under the model

$$\boldsymbol{y}_{ij} - \tilde{\tilde{\gamma}}_i \mathbf{1}_p = \boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\phi}) + (\text{error}).$$

iii) Set $\tilde{Z} = Z(\tilde{\boldsymbol{\phi}})$ and treat as a known matrix. Let

$$\tilde{\boldsymbol{e}}_{ij} = \boldsymbol{y}_{ij} - \tilde{\bar{\gamma}}_i \mathbf{1}_p - \boldsymbol{f}(\boldsymbol{t}; \tilde{\boldsymbol{\phi}}),\ \tilde{\boldsymbol{b}}_{ij} = (\tilde{Z}'\tilde{Z})^{-1}\tilde{Z}'\tilde{\boldsymbol{e}}_{ij},$$

and

$$\tilde{s}_{ij}^2 = \tilde{\boldsymbol{e}}_{ij}'\{I_p - \tilde{Z}(\tilde{Z}'\tilde{Z})^{-1}\tilde{Z}'\}\tilde{\boldsymbol{e}}_{ij}/(p-q).$$

iv) Obtain estimates of σ^2 and Ψ as

$$\hat{\sigma}^2 = \sum_{i,j} \tilde{s}_{ij}^2/kn \quad \text{and} \quad \hat{\Psi} = S_b - \{\min(\hat{\sigma}^2, \hat{\lambda})\}(\tilde{Z}'\tilde{Z})^{-1},$$

respectively, where $S_b = \sum_{i,j} \tilde{\boldsymbol{b}}_{ij}\tilde{\boldsymbol{b}}_{ij}'/kn$ and $\hat{\lambda}$ is the minimum root of

$$\left| S_b - \lambda(\tilde{Z}'\tilde{Z})^{-1} \right| = 0.$$

v) Obtain the EGLS $\hat{\boldsymbol{\phi}}$ by minimizing

$$\sum_{i,j} \{\boldsymbol{y}_{ij} - \tilde{\gamma}_i \mathbf{1}_p - \boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\phi})\}' \tilde{\Sigma}^{-1} \{\boldsymbol{y}_{ij} - \tilde{\gamma}_i \mathbf{1}_p - \boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\phi})\}, \tag{3}$$

where $\tilde{\Sigma} = \tilde{Z}\hat{\Psi}\tilde{Z}' + \hat{\sigma}^2 I_p$ and

$$\tilde{\gamma}_i = \mathbf{1}_p'\tilde{\Sigma}^{-1}(\bar{\boldsymbol{y}}_i - \bar{\boldsymbol{y}}_.)/\mathbf{1}_p'\tilde{\Sigma}^{-1}\mathbf{1}_p \qquad (i = 1, \ldots, k).$$

vi) Obtain the estimate

$$\hat{\gamma}_i = \mathbf{1}_p' W^{-1}(\bar{\boldsymbol{y}}_i - \bar{\boldsymbol{y}}_.)/\mathbf{1}_p' W^{-1}\mathbf{1}_p \qquad (i = 1, \ldots, k),$$

where $W = \sum_{i,j} \{\boldsymbol{y}_{ij} - \tilde{\gamma}_i \mathbf{1}_p - \boldsymbol{f}(\boldsymbol{t}; \hat{\boldsymbol{\phi}})\}\{\boldsymbol{y}_{ij} - \tilde{\gamma}_i \mathbf{1}_p - \boldsymbol{f}(\boldsymbol{t}; \hat{\boldsymbol{\phi}})\}'$.

We note that the EGLS $\hat{\boldsymbol{\phi}}$ obtained in v) also minimizes

$$\sum_{i,j} \{\boldsymbol{y}_{ij} - \boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\phi})\}' \tilde{\Sigma}^{-1} \{\boldsymbol{y}_{ij} - \boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\phi})\}$$

by $\sum_i \tilde{\gamma}_i = 0$. The distribution of $\hat{\boldsymbol{\phi}}$ is $N_q\big(\boldsymbol{\phi}, (Z'\Sigma^{-1}Z)^{-1}/nk\big)$ by B a b a et al [1]. The difference of $\tilde{\gamma}_i$ in v) and $\hat{\gamma}_i$ in iv) will not be large if $\tilde{\Sigma}$ is positive definite. Let $\hat{\boldsymbol{f}} = \boldsymbol{f}(\boldsymbol{t}; \hat{\boldsymbol{\phi}})$ and $Y = [\bar{\boldsymbol{y}}_i - \bar{\boldsymbol{y}}_. - \hat{\gamma}_1 \mathbf{1}_p, \ldots, \bar{\boldsymbol{y}}_k - \bar{\boldsymbol{y}}_. - \hat{\gamma}_k \mathbf{1}_p]$, then we have

$$W \approx \sum_{i,j} (\boldsymbol{y}_{ij} - \hat{\gamma}_i \mathbf{1}_p - \hat{\boldsymbol{f}})(\boldsymbol{y}_{ij} - \hat{\gamma}_i \mathbf{1}_p - \hat{\boldsymbol{f}})' = V + nk(\bar{\boldsymbol{y}}_. - \hat{\boldsymbol{f}})(\bar{\boldsymbol{y}}_. - \hat{\boldsymbol{f}})' + nYY'. \tag{4}$$

By using the binomial inverse theorem (see, e.g., S i o t a n i et al. [6]), it is easy see that

$$\mathbf{1}_p' W^{-1} = \mathbf{1}_p' \{V + nk(\bar{\boldsymbol{y}}_. - \hat{\boldsymbol{f}})(\bar{\boldsymbol{y}}_. - \hat{\boldsymbol{f}})'\}^{-1}. \tag{5}$$

But $\tilde{\gamma}_i$ may not be stable, since $\tilde{\gamma}_i$'s in v) depend on $S_b - \{\min(\hat{\sigma}^2, \hat{\lambda})\}(\tilde{Z}'\tilde{Z})^{-1}$, which is not always positive definite. In the next section we find that $\hat{\gamma}_i$ is better

than $\tilde{\gamma}_i$. So we use the estimator $\hat{\gamma}_i$ for construction of simultaneous confidence intervals of $\gamma_i - \gamma_{i'}$ $(i < i')$, whose estimators are

$$\hat{\gamma}_i - \hat{\gamma}_{i'} = \mathbf{1}_p' W^{-1}(\bar{\boldsymbol{y}}_i - \bar{\boldsymbol{y}}_{i'})/\mathbf{1}_p' W^{-1}\mathbf{1}_p \qquad (i < i'). \tag{6}$$

Hence the comparisons of γ_i's are based on $\bar{\boldsymbol{y}}_i$'s. Here we treat W in (6) as Σ, then $\mathbf{1}_p'\Sigma^{-1}(\bar{\boldsymbol{y}}_i - \bar{\boldsymbol{y}}_\cdot)/\mathbf{1}_p'\Sigma^{-1}\mathbf{1}_p$ has $N\big(\gamma_i, (k-1)/(nk\mathbf{1}_p'\Sigma^{-1}\mathbf{1}_p)\big)$. So the distribution of $\hat{\gamma}_i$ would be approximated by $N\big(\gamma_i, (k-1)/(nk\mathbf{1}_p'\Sigma^{-1}\mathbf{1}_p)\big)$ and Tukey's method would be used to construct simultaneous confidence intervals for pairwise comparisons. Next we consider about the distribution of $\mathbf{1}_p' W^{-1}\mathbf{1}_p$ which is an estimator of $\mathbf{1}_p'\Sigma^{-1}\mathbf{1}_p$. Since the distribution of $\boldsymbol{y}_{ij}$ is approximately normal, V has a Wishart distribution with the covariance matrix Σ and $k(n-1)$ degrees of freedom (d.f.), approximately. By a method similar to that of Baba et al. [1], $nk(\bar{\boldsymbol{y}}_\cdot - \hat{\boldsymbol{f}})(\bar{\boldsymbol{y}}_\cdot - \hat{\boldsymbol{f}})'$ may be approximated by a Wishart distribution with the covariance matrix $\Sigma - Z(Z'\Sigma^{-1}Z)^{-1}Z'$ and 1 df. So the approximate d.f. of W are $k(n-1)$. Hence the distribution of $\mathbf{1}_p'\Sigma^{-1}\mathbf{1}_p/\mathbf{1}_p' W^{-1}\mathbf{1}_p$ is approximated by χ^2_ν by Corollary 2.4.5.1 of Siotani et al. [6], where $\nu = k(n-1) - p + 1$. Then the simultaneous confidence intervals are approximated by

$$\gamma_i - \gamma_{i'} \in \hat{\gamma}_i - \hat{\gamma}_{i'} \pm q^* \sqrt{(2/n)(\mathbf{1}_p' W^{-1}\mathbf{1}_p)^{-1}/\nu} \qquad (i < i'), \tag{7}$$

where q^* is the $100\alpha\,\%$ point of the Studentized range distribution and is tabulated in Hsu [4].

3. Simulation and example

Approximate simultaneous confidence intervals are given in the previous section. In this section, we examine the accuracy of approximation by simulation and give a numerical example by using part of data tabulated in Davis [3].

3.1. Simulation

Three models:

Model I: $f(t;\boldsymbol{\phi}) = \phi_1 + \phi_2 t$,

$$(\phi_1, \phi_2) = (6.0, -1.0), \quad \varepsilon \sim N(0, 0.4), \quad \boldsymbol{b} \sim N_2\left(\mathbf{0}; \begin{pmatrix} 0.3 & 0.1 \\ 0.1 & 0.1 \end{pmatrix}\right);$$

Model II: $f(t;\boldsymbol{\phi}) = \phi_1 e^{-\phi_2 t}$

$$(\phi_1, \phi_2) = (5.0, 0.5), \quad \varepsilon \sim N(0, 0.1), \quad \boldsymbol{b} \sim N_2\left(\mathbf{0}; \begin{pmatrix} 0.16 & 0.04 \\ 0.04 & 0.04 \end{pmatrix}\right);$$

Model III: $f(t;\boldsymbol{\phi}) = 2/(1 + \phi_1 e^{-\phi_2 t})$

$$(\phi_1, \phi_2) = (2.0, 0.8), \quad \varepsilon \sim N(0, 0.1), \quad \boldsymbol{b} \sim N_2\left(\mathbf{0} \begin{pmatrix} 0.60 & 0.08 \\ 0.08 & 0.04 \end{pmatrix}\right)$$

are used in the simulation. For each population, we choose the level difference parameters $\gamma_1 = 0.0,\ \gamma_2 = 1.0,\ \gamma_3 = -1.0,\ \gamma_4 = 0.0$. We use $(\gamma_1, \gamma_2, \gamma_3)$ and $(\gamma_1, \gamma_2, \gamma_3, \gamma_4)$ for $k = 3$ and $k = 4$, respectively. The observed points are $t = 1, 2, 3, 4$ $(p = 4)$ and the sample sizes from each population are $n = 8, 14, 20$. For each case, 10,000 replications were carried out. We compare the estimators $\tilde{\gamma}$ and $\hat{\gamma}$ by computing the estimated mean square errors (MSE). The results in Table 1 show that $\hat{\gamma}$ is better than $\tilde{\gamma}$.

Table 1. Comparison of MSE.

		$k = 3$		$k = 4$	
Model	n	$\tilde{\gamma}$	$\hat{\gamma}$	$\tilde{\gamma}$	$\hat{\gamma}$
(I)	8	0.3669	0.2424	0.4937	0.3444
	14	0.2068	0.1283	0.2846	0.1909
	20	0.1436	0.0872	0.2320	0.1302
(II)	8	0.2367	0.1096	0.1863	0.1735
	14	0.1390	0.0573	0.2029	0.0862
	20	0.0973	0.0401	0.1362	0.0587
(III)	8	0.0100	0.0051	0.0776	0.0087
	14	0.0054	0.0029	0.0044	0.0043
	20	0.0033	0.0020	0.0029	0.0029

Next, we examine the accuracy of approximation of (7). For each case in the above and $\alpha = 0.05$, 10,000 pairwise intervals were constructed. The proportion of times that all of 3 (when $k = 3$) or 6 (when $k = 4$) pairwise confidence intervals include the true values $\gamma_i - \gamma_{i'}$, is calculated. The results are in Table 2. From Table 2, the approximation would be good except for the case $(k, n) = (3, 8)$ of Model II.

Table 2. Accuracy of approximation.

	(I)		(II)		(III)	
n	$k = 3$	$k = 4$	$k = 3$	$k = 4$	$k = 3$	$k = 4$
8	0.9466	0.9501	0.9647	0.9466	0.9427	0.9426
14	0.9447	0.9471	0.9547	0.9527	0.9429	0.9454
20	0.9474	0.9510	0.9488	0.9563	0.9451	0.9482

3.2. Numerical example

We give a numerical example by using the data in Table 3, which are part of the plasma inorganic phosphate measurements, tabulated in Davis [3].

The observations taken at 0, 0.5, 1.0, and 1.5 hours after a standard-dose glucose challenge. In this table, Ctrl, NH, and HY are control, nonhyperinsulimic obese, and hyperinsulimic patients, respectively.

TABLE 3. Plasma inorganic phosphate levels.

	Ctrl				NH				HY			
	0.0	0.5	1.0	1.5	0.0	0.5	1.0	1.5	0.0	0.5	1.0	1.5
1	4.3	3.3	3.0	2.6	4.3	3.3	3.0	2.6	4.9	4.3	4.0	4.0
2	3.7	2.6	2.6	1.9	5.0	4.9	4.1	3.7	5.1	4.1	4.6	4.1
3	4.0	4.1	3.1	2.3	4.6	4.4	3.9	3.9	4.8	4.6	4.6	4.4
4	3.6	3.0	2.2	2.8	4.3	3.9	3.1	3.1	4.2	3.5	3.8	3.6
5	4.1	3.8	2.1	3.0	3.1	3.1	3.3	2.6	6.6	6.1	5.2	4.1
6	3.8	2.2	2.0	2.6	4.8	5.0	2.9	2.8	3.6	3.4	3.1	2.8
7	3.8	3.0	2.4	2.5	3.7	3.1	3.3	2.8	4.5	4.0	3.7	3.3
8	4.4	3.9	2.8	2.1	5.4	4.7	3.9	4.1	4.6	4.4	3.8	3.8
$\bar{x}$	3.96	3.24	2.53	2.48	4.40	4.05	3.44	3.20	4.79	4.30	4.10	3.76

We assume the model $f(t;\boldsymbol{\phi}) = \phi_1 e^{-\phi_2 t}$, which is one of the models assumed in the simulation, for the data.

$$(\hat{\phi}_1, \hat{\phi}_2) = (4.352,\ 0.2325), \quad \hat{\sigma}^2 = 0.1311, \quad \hat{\Psi} = \begin{pmatrix} 0.5275 & 0.0409 \\ 0.0409 & 0.0088 \end{pmatrix},$$

$$(\hat{\gamma}_1, \hat{\gamma}_2, \hat{\gamma}_3) = (-0.7714,\ 0.0702,\ 0.7012).$$

Then the 95 % simultaneous confidence intervals are

$$-1.003 < \gamma_1 - \gamma_2 < -0.680,\ -1.634 < \gamma_1 - \gamma_3 < -1.311,\ -0.793 < \gamma_2 - \gamma_3 < -0.470.$$

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