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Pairwise Comparisons in Nonlinear Repeated Measurements

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1. Introduction

Let $\boldsymbol{y}_{ir} = (y_{ir,1}, \cdots, y_{ir,p})'$ be a p dimensional observation from the i-th population ($i = 1, \cdots, k$, $r = 1, \cdots, n_i$). 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 $\boldsymbol{\beta}_i = (\beta_{i1}, \cdots, \beta_{iq})'$ is unknown parameter ($q \leq p$). Let $\boldsymbol{f}_i = (f(t_1; \boldsymbol{\beta}_i), \cdots, f(t_p; \boldsymbol{\beta}_i))'$, then $\boldsymbol{y}_{ir} = \boldsymbol{f}_i + \boldsymbol{\varepsilon}_{ir}$, where $\boldsymbol{\varepsilon}_{ir} = (\varepsilon_{ir,1}, \cdots, \varepsilon_{ir,p})'$. Suppose that $E[\boldsymbol{\varepsilon}_{ir}] = \mathbf{0}$, $\mathrm{Var}[\boldsymbol{\varepsilon}_{ir}] = \boldsymbol{\Sigma}$, 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 (1989). In Section 3, the accuracy of approximation by Taylor expansion is examined by simulation. The numerical example by histamine data is given in Section 4.

A nonlinear model $(\theta_1/(\theta_2 - \theta_3))(e^{-\theta_3 t} - e^{-\theta_2 t})$, $(\theta_2 > \theta_3)$ is usually used for pharmacokinetic data, where θ_1, θ_2 and θ_3 are unknown parameters, see e.g. Lindsey et. al. (2000) or Section 5.5 of Davidian and Giltinan (1995). In this model, θ_2 and θ_3 are the absorption and elimination rate parameters, respectively. If $\theta_3 \to \theta_2$, then the model tends to $\theta_1 t e^{-\theta_2 t}$ However, the value at time $t = 0$ is 0 in this model. For histamine data described in Section 4, the mean may not be 0 at $t = 0$, we assume the model

$$f(t; \beta_i) = \beta_{i1} + \beta_{i2} t e^{-\beta_{i3} t}. \tag{1.1}$$

Our interest is the maximum value of this model, because the possibility of allergic response is large for high histamine value. Hence we would like to compare

$$g_i = g(\boldsymbol{\beta}_i) = \max_t f(t;\boldsymbol{\beta}_i) = \beta_{i1} + \frac{\beta_{i2}}{\beta_{i3}} e^{-1}, \tag{1.2}$$

by constructing the simultaneous confidence intervals of the differences.

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 $\hat{\boldsymbol{f}}_i = (f(t_1;\hat{\boldsymbol{\beta}}_i), \cdots, f(t_p;\hat{\boldsymbol{\beta}}_i))'$. 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

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

and

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

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

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

where $\bar{\boldsymbol{\varepsilon}}_i = \sum_r \boldsymbol{\varepsilon}_{ir}/n_i$ and $\boldsymbol{P}_{F_i} = \boldsymbol{F}_{\cdot}^{(i)}(\boldsymbol{F}_{\cdot}^{(i)\prime}\boldsymbol{F}_{\cdot}^{(i)})^{-1}\boldsymbol{F}_{\cdot}^{(i)\prime}$. If $\boldsymbol{\varepsilon}_{ir}$ has the p-variate normal distribution, $N_p(\mathbf{o}, \boldsymbol{\Sigma})$, then $(\boldsymbol{F}_{\cdot}^{(i)\prime}\boldsymbol{F}_{\cdot}^{(i)})^{-1}\boldsymbol{F}_{\cdot}^{(i)\prime}\sum_r \boldsymbol{\varepsilon}_{ir}/n_i$ has $N_k\big(\mathbf{o}, (\boldsymbol{F}_{\cdot}^{(i)\prime}\boldsymbol{F}_{\cdot}^{(i)})^{-1}\boldsymbol{F}_{\cdot}^{(i)\prime}\boldsymbol{\Sigma}\boldsymbol{F}_{\cdot}^{(i)}$

$(\boldsymbol{F}_{\cdot}^{(i)'}\boldsymbol{F}_{\cdot}^{(i)})^{-1}/n_i\Big)$ and $g_{i\cdot}'(\hat{\boldsymbol{\beta}}_i - \boldsymbol{\beta}_i)$ has $N\Big(0,\ g_{i\cdot}'(\boldsymbol{F}_{\cdot}^{(i)'}\boldsymbol{F}_{\cdot}^{(i)})^{-1}\boldsymbol{F}_{\cdot}^{(i)'}\boldsymbol{\Sigma}\boldsymbol{F}_{\cdot}^{(i)}(\boldsymbol{F}_{\cdot}^{(i)'}\boldsymbol{F}_{\cdot}^{(i)})^{-1}\boldsymbol{g}_{i\cdot}/n_i\Big)$. $\hat{\boldsymbol{\beta}}_i$ 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 $\boldsymbol{F}_{\cdot}^{(i)'}(\boldsymbol{I}_p - \boldsymbol{P}_{F_i}) = \boldsymbol{O}$, $\boldsymbol{F}_{\cdot}^{(i)'}\boldsymbol{V}_i\boldsymbol{F}_{\cdot}^{(i)}$ has a Wishart distribution with covariance matrix $\boldsymbol{F}_{\cdot}^{(i)'}\boldsymbol{\Sigma}\boldsymbol{F}_{\cdot}^{(i)}$ and $n_i - 1$ degrees of freedom, $W_k(\boldsymbol{F}_{\cdot}^{(i)'}\boldsymbol{\Sigma}\boldsymbol{F}_{\cdot}^{(i)},\ n_i - 1)$, approximately. Hence the distribution of $\boldsymbol{V} = \boldsymbol{V}_1 + \cdots + \boldsymbol{V}_k$ would be approximated by $W_p(\boldsymbol{\Sigma},\ \nu)$, where $\nu = n_1 + \cdots + n_k - k$. 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 $\boldsymbol{a}_i = \boldsymbol{F}_{\cdot}^{(i)}(\boldsymbol{F}_{\cdot}^{(i)'}\boldsymbol{F}_{\cdot}^{(i)})^{-1}\boldsymbol{g}_{i\cdot}$. We propose the following simultaneous confidence intervals for all pairwise differences:

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

where q is the solution to the equation

$$\begin{aligned} &P\Big(\frac{\sqrt{\nu}|(\hat{g}_i - \hat{g}_{i'}) - (g_i - g_{i'})|}{\sqrt{\boldsymbol{a}_i'\boldsymbol{V}\boldsymbol{a}_i/n_i + \boldsymbol{a}_{i'}'\boldsymbol{V}\boldsymbol{a}_{i'}/n_{i'}}} < q,\ \text{for all } i \neq i'\Big) \\ &= E_V\Big[P\Big(\frac{|(\hat{g}_i - \hat{g}_{i'}) - (g_i - g_{i'})|}{\sqrt{\boldsymbol{a}_i'\boldsymbol{\Sigma}\boldsymbol{a}_i/n_i + \boldsymbol{a}_{i'}'\boldsymbol{\Sigma}\boldsymbol{a}_{i'}/n_{i'}}} < \frac{q}{\sqrt{\nu}}\sqrt{\frac{\boldsymbol{a}_i'\boldsymbol{V}\boldsymbol{a}_i/n_i + \boldsymbol{a}_{i'}\boldsymbol{V}\boldsymbol{a}_{i'}/n_{i'}}{\boldsymbol{a}_i'\boldsymbol{\Sigma}\boldsymbol{a}_i/n_i + \boldsymbol{a}_{i'}'\boldsymbol{\Sigma}\boldsymbol{a}_{i'}/n_{i'}}},\ \text{for all } i \neq i'\ |V\Big)\Big] \\ &= 1 - \alpha. \end{aligned} \tag{2.4}$$

However, we can not solve the equation (2.4), because (2.4) depends on the unknown parameters, Σ and $\boldsymbol{a}_i$. Let $(\boldsymbol{a}_i'\boldsymbol{V}\boldsymbol{a}_i/n_i + \boldsymbol{a}_{i'}'\boldsymbol{V}\boldsymbol{a}_{i'}/n_{i'})/(\boldsymbol{a}_i'\boldsymbol{\Sigma}\boldsymbol{a}_i/n_i + \boldsymbol{a}_{i'}'\boldsymbol{\Sigma}\boldsymbol{a}_{i'}/n_{i'}) = w_{ii'}$.

Now, we may approximate all statistics $w_{ii'}$ by a same statistic w distributed as χ^2_ν, 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. Since $\boldsymbol{a}_i = \boldsymbol{F}_{\cdot}^{(i)}(\boldsymbol{F}_{\cdot}^{(i)'}\boldsymbol{F}_{\cdot}^{(i)})^{-1}\boldsymbol{g}_{i\cdot}$ in (2.3) includes unknown parameter $\boldsymbol{\beta}_i$, 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) is used in the simulation. We compare the maximum values (1.2) in model (1.1) with known $\beta_{i1} = 0$. We choose the parameters for 3 populations ($k = 3$) as follows:

Table 1. Models and Parameters

Model (f_i) max f_i (g_i)	$\beta_{i2}te^{-\beta_{i3}t}$ ($\beta_{i2}e^{-1}/\beta_{i3}$)		
Population (i)	1	2	3
β_{i2}	0.8	0.9	1.0
β_{i3}	0.6	0.5	0.4

The observed points are $t = 1, 2, 3, 4$ ($p = 4$) for both models and the sample sizes from each population are $n_i = 8, 12, 16$ ($i = 1, 2, 3$). The error has the normal distribution with mean $\mathbf{o}$ and covariance matrix Σ_ℓ ($\ell = 1, 2$), where

$$\Sigma_1 = 0.1^2 I,\ \Sigma_2 = \text{diag}(0.08^2, 0.10^2, 0.10^2, 0.08^2).$$

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).

Table 2. Accuracy of Approximation

	Σ_1	Σ_2
8	.9655 (.9416)	.9601 (.9443)
12	.9590 (.9516)	.9583 (.9431)
16	.9592 (.9504)	.9576 (.9424)

From Table 2, 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 somewhat less than 0.95 under the small sample size.

4. An Example

We give a numerical example by using histamine data in dental anesthesiology. The past allergic patients are given medicine, Atropine + Hydroxydine (AH), Atropine + Chlorpheniramine (AC), or Atropine + Famotidine (AF), before anethesia. Usually, the histamine values of allergic patients are large after anethesia, but the values are decrease by dosing AH, AC, or AF. The data $\boldsymbol{y}$ are measured at (0.0, 0.5, 1.0, 3.0, 5.0) minutes after anethesia, that is $p = 5$. The values of observations are Tables 3a, 3b, and 3c. We wish to know the difference of the effect to histamine value by AH, AC, and AF. The sample sizes are $n_1 = 18, n_2 = 18, n_3 = 19$, that is, $\nu = 52$. We assume the model (1.1) for histamine data and construct simultaneous confidence intervals of $g_i - g_{i'}$, where g_i is given in (1.2).

Table 3a. Atropine+Hydroxydine

	0min.	0.5min.	1min.	3min.	5min.
1	0.125	0.141	0.096	0.093	0.068
2	0.279	0.423	0.919	0.155	0.857
3	0.466	0.508	0.450	0.219	0.412
4	0.219	0.535	0.213	0.298	0.105
5	0.281	0.285	0.312	0.162	0.151
6	0.385	0.526	0.367	0.201	0.275
7	0.386	0.351	0.327	0.133	0.210
8	0.175	0.184	0.173	0.368	0.372
9	0.194	0.283	0.168	0.231	0.169
10	0.138	0.155	0.173	0.144	0.125
11	0.371	1.458	0.572	1.070	0.304
12	0.136	0.207	0.184	0.118	0.264
13	0.515	0.587	0.505	0.595	0.551
14	0.473	0.292	0.531	0.429	0.515
15	0.446	0.445	0.372	0.478	0.551
16	0.144	0.147	0.227	0.368	0.105
17	0.621	0.646	0.686	0.567	0.580
18	0.424	0.385	0.330	0.279	0.367

Table 3b. Atropine+Chlorpheniramine

	0min.	0.5min.	1min.	3min.	5min.
1	0.362	0.468	0.371	0.353	0.462
2	0.145	0.086	0.229	0.095	0.136
3	0.213	0.169	0.207	0.200	0.015
4	0.432	0.669	0.548	0.525	0.386
5	0.292	0.616	0.749	0.445	0.465
6	0.434	0.296	0.481	0.505	0.533
7	0.647	0.093	0.108	0.079	0.076
8	0.937	0.916	0.677	0.760	0.728
9	0.377	0.314	0.459	0.172	0.154
10	0.396	0.514	0.332	0.557	0.496
11	0.327	0.403	0.453	0.527	0.233
12	0.406	0.532	0.199	0.484	0.163
13	0.189	0.398	0.340	0.213	0.269
14	0.247	0.172	0.106	0.113	0.158
15	0.689	1.302	0.633	0.655	0.782
16	0.834	0.653	0.596	0.371	0.387
17	0.472	0.435	0.503	0.393	0.384
18	0.741	0.644	0.668	0.835	0.763

Table 3c. Atropine+Famotidine

	0min.	0.5min.	1min.	3min.	5min.
1	0.151	0.171	0.126	0.154	0.217
2	0.242	0.318	0.155	0.270	0.368
3	0.308	0.155	0.132	0.095	0.256
4	0.220	0.275	0.265	0.289	0.251
5	0.217	0.255	0.127	0.112	0.261
6	0.440	1.057	0.872	0.551	0.898
7	0.366	0.210	0.298	0.237	0.326
8	0.255	0.148	0.105	0.153	0.135
9	0.170	0.517	0.330	0.963	0.551
10	0.350	0.416	0.403	0.425	0.365
11	0.849	1.229	1.621	0.621	0.828
12	0.327	0.157	0.203	0.216	0.234
13	0.503	1.001	0.814	0.912	0.579
14	0.247	0.250	0.615	0.473	0.285
15	0.657	0.822	0.592	0.907	0.780
16	0.706	0.340	0.186	0.254	0.262
17	0.553	0.479	0.484	0.429	0.414
18	0.456	0.467	0.535	0.490	0.494
19	0.447	0.744	1.126	0.522	0.456

The estimates are calcurated as follows:

$$\begin{aligned}
\text{AP:} &\quad \hat{f}_1 = 0.327 + 0.863t\exp(-3.075t), \quad \hat{g}_1 = 0.4304\ (t = 0.325),\\
\text{AC:} &\quad \hat{f}_2 = 0.408 + 1.246t\exp(-4.245t), \quad \hat{g}_2 = 0.5156\ (t = 0.236),\\
\text{AF:} &\quad \hat{f}_3 = 0.404 + 0.236t\exp(-1.169t), \quad \hat{g}_3 = 0.4781\ (t = 0.855),
\end{aligned}$$

and

$$\boldsymbol{S} = \begin{pmatrix} 0.0382 & 0.0364 & 0.0322 & 0.0223 & 0.0255 \\ & 0.0993 & 0.0664 & 0.0602 & 0.0477 \\ & & 0.0839 & 0.0390 & 0.0479 \\ & & & 0.0613 & 0.0352 \\ & & & & 0.0504 \end{pmatrix}.$$

Let us take $\alpha = 0.05$, then $q = 2.413$, which is obtained by interpolating of the values for $\nu = 50$ and 60 of Table E.1 in Hsu (1996). Hence the simultaneous confidence intervals for all-pairwise differences are obtained in Table 4.

Table 4. Confidence Intervals

$g_1 - g_2$	-0.5994, 0.4290
$g_1 - g_2$	-0.4232, 0.3278
$g_2 - g_3$	-0.3806, 0.4556

From Table 4, all intervals are include 0, that is the maximum values are not statistically different.

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