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MULTIVARIATE ANALYSIS OF REPEATED MEASURES DATA

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ABSTRACT

In this paper, we have used SAS software for the multivariate analysis of repeated measures data due to Grizzel and Allen (1969). We have applied four multivariate methods viz MANOVA, Profile Analysis, non-parametric multisample rank sum test and non-parametric multisample median test to analyse two sets of data. The findings of the study reveal that profile analysis gives similar results as revealed by MANOVA, except in case of Pillai's trace and Hotelling-Lowley's trace statistics where time*group effects were found insignificant. Non-parametric analysis of the same data revealed different conclusions.

KEY WORDS: Repeated measures, ANOVA, MANOVA, Profile analysis, Non-parametric, Multiple sample.

1. INTRODUCTION

Many methods have been used for the analysis of repeated measures data. The classical approach is to treat the experimental units in a repeated measures study as blocks in a blocked design. Multivariate approaches make fewer assumptions than the classical approach, but in general are less powerful when the assumptions that the classical approach requires are met. The newest approach uses mixed models, which may not require as stringent assumptions as the classical approach and under some circumstances may be more powerful and flexible than the multivariate approach. In this paper, we define some multivariate methods for repeated measures, and discuss their analysis with SAS software. Some researchers have also done some useful work in this area.

Cole and Grizzle (1966) have provided the use of MANOVA (multivariate analysis of variance) for the analysis of repeated measurement experiments as the successive observations of the same variable are supposed to be correlated. Khatri (1966) presented a note on a MANOVA model applicable to the problems in growth curves for repeated measures data. Wang et al. (2006) fitted a mixed model with repeated measurements using SAS to determine the optimum test duration and the effect of missing data on accuracy of measuring feed efficiency and its four related traits ADG, DMI, feed conversion ratio, and residual feed intake in beef cattle by repeated measurements. Mendes et al. (2007) used the methods of profile analysis and growth curve analysis to investigate the effect of different feed restrictions applied in

early period on changes of Body Mass Index of Ross 308 broiler chickens. Profile analysis was used to compare differences among the groups and the Gompertz growth function was regressed from these data to estimate the growth parameters. Tiwari and Shukla (2011) have used the approach of linear mixed model for the analysis of longitudinal data using SAS software.

2. MATERIALS AND METHODS

2.1 Multivariate Analysis of Variance (MANOVA)

Multivariate analysis of variance (MANOVA) is used to test the equality of mean vectors of several multivariate normal populations. The main objective of using MANOVA in repeated measurement is to avoid sphericity assumptions.

In this case mathematical linear model will be

$$Y = XB + E \tag{1}$$

Where, Y denotes the n×t data matrix.
X denotes the n×k known design matrix.
B denotes the k×t parameter matrix.
E denotes the n×t matrix of random error.
n denotes the total number of experimental units.
t denotes total time points.
k denotes number of groups in the data.

Statistical Analysis of Model (1.1)

Hypotheses

$$H_0 : \underline{\mu}^1 = \underline{\mu}^2 = \ldots\ldots\ldots\ldots = \underline{\mu}^k$$

$$H_1 : \underline{\mu}^1 \neq \underline{\mu}^2 = \ldots\ldots\ldots\ldots = \underline{\mu}^k$$

Test Statistic

$$\Lambda = \frac{|W|}{|W+Q|} \tag{2}$$

This statistic is known as Wilks' Λ.

Where $$W = \sum_{i=1}^{k}\sum_{\alpha=1}^{n_i}(\underline{x}_\alpha^i - \underline{\mu}^i)(\underline{x}_\alpha^i - \underline{\mu}^i)'$$

$$Q = \sum_{i=1}^{k} n_i(\underline{\mu}^i - \underline{\mu})(\underline{\mu}^i - \underline{\mu})' \tag{3}$$

After calculating Wilks' Λ, we use Bartlett's χ^2 - statistic for testing null hypothesis given by

$$\chi^2 = -(n-1-\frac{t+k}{2})\log_e \Lambda \sim \chi^2_{\frac{t(t+1)(k-1)}{2}} \tag{4}$$

We reject H_0 at α level of significance if $\chi^2 > \chi^2_{\frac{t(t+1)(k-1)}{2},\alpha}$; otherwise accept H_0.

Source of variation	df	sum of product matrix	Λ
Between Groups	(k-1)	$Q = \sum_{i=1}^{k} n_i (\underline{\mu}^i - \underline{\mu})(\underline{\mu}^i - \underline{\mu})'$	$\frac{\lvert W \rvert}{\lvert W + Q \rvert}$
Within Groups	(n-k)	$W = \sum_{i=1}^{k}\sum_{\alpha=1}^{n_i} (\underline{x}_\alpha^i - \underline{\mu}^i)(\underline{x}_\alpha^i - \underline{\mu}^i)'$	
Total	(n-1)	$Q+W = \sum_{i=1}^{k}\sum_{\alpha=1}^{n_i} (\underline{x}_\alpha^i - \underline{\mu})(\underline{x}_\alpha^i - \underline{\mu})'$	

Table 1: MANOVA Table

2.2 Profile Analysis

Profile analysis is the multivariate equivalent of repeated measures or mixed ANOVA. Profile analysis is most commonly used in two cases:
1) Comparing the same dependent variables between groups over several time-points.
2) When there are several measures of the same dependent variable (Ex. several different psychological tests that all measure depression).

Profile analysis uses plots of the data to visually compare across groups. Following this, specific equations can be used to test for the significance of the various patterns or effects.

Let us assume that repeated measurements at t time points have been obtained from s groups of subjects. n_h denotes the number of subjects in group h for h=1,2,...,s and $n = \sum_{h=1}^{s} n_h$ denote the total sample size. Y_{hij} denotes the response at time j from the ith subject in group h for h=1,2,…,s, i=1,2,…,n_h and j=1,2,…,t. The data vectors $\mathbf{y_{hi}} = (y_{hi1},\ldots,y_{hit})'$ are independent and normally distributed with mean $\boldsymbol{\mu_h} = (\mu_{h1},\ldots,\mu_{ht})'$ and common covariance matrix Σ.
Thus $\mathbf{y_{hi}} \sim N_t(\boldsymbol{\mu_h}, \Sigma)$.
Thus the Profile Analysis model is:

$$Y_{hij} = \mu_{hj} + e_{hij} \quad (5)$$

where e_{hij} is the residual for subject i in group h at time j. The vector $\mathbf{e_{hi}} = (e_{hi1},\ldots\ldots\ldots,e_{hit})$ is the vector of residuals for the i^{th} subject in group h.
Three general hypotheses are of interest in profile analysis:

H_{01} : The profiles for the s groups are parallel.
H_{02} : No differences among groups.
H_{03} : No differences among time points.

2.2.1 Test of Parallelism

The hypothesis of parallelism is:

$$H_{01}: \begin{pmatrix} \mu_{11} - \mu_{12} \\ \mu_{12} - \mu_{13} \\ \mu_{1,t-1} - \mu_{1t} \end{pmatrix} = \begin{pmatrix} \mu_{21} - \mu_{22} \\ \mu_{22} - \mu_{23} \\ \mu_{2,t-1} - \mu_{2t} \end{pmatrix} = \ldots\ldots = \begin{pmatrix} \mu_{s1} - \mu_{s2} \\ \mu_{s2} - \mu_{s3} \\ \mu_{s,t-1} - \mu_{st} \end{pmatrix} \quad (6)$$

Testing this hypothesis is equivalent to carry out a multivariate analysis of variance (MANOVA) model on the (t-1) differences between adjacent time points from each sampling unit.

2.2.2 Tests of No Differences Among Groups

If the parallelism hypothesis is reasonable, the test for differences among groups can be carried out using the sum (or average) of the repeated observations from each subject. Because the s groups are independent, this test of H_{02} is equivalent to that from a one-way ANOVA on the totals (or means) across time from each subject.

In this case null the hypothesis is:

$H_{02}: ABC = D$

Where $A_{(s-1)\times s} = (I_{s-1}, -\mathbf{1}_{s-1})$

$C_{t\times t} = I_t$

$D_{(s-1)x1} = \mathbf{0}_{s-1}$

A multivariate test for differences among groups can also be carried out without assuming parallelism. In this case null the hypothesis is:

$$H_{02}: \begin{pmatrix} \mu_{11} \\ \mu_{12} \\ . \\ \mu_{1t} \end{pmatrix} = \begin{pmatrix} \mu_{21} \\ \mu_{22} \\ . \\ \mu_{2t} \end{pmatrix} = \ldots\ldots\ldots = \begin{pmatrix} \mu_{s1} \\ \mu_{s2} \\ . \\ \mu_{st} \end{pmatrix}$$

or

In term of general hypothesis; $H_{02}: ABC = D$

where $A_{(s-1)\times s} = (I_{s-1}, -\mathbf{1}_{s-1})$

$C_{t\times t} = I_t$

$$D_{(s-1)\times t} = \begin{pmatrix} 0\ldots\ldots\ldots 0 \\ 0\ldots\ldots\ldots 0 \end{pmatrix}$$

If the comparisons among groups for a subset of the t time points are of interest, the columns of C corresponding to the excluded time points can be omitted.

2.2.3 Tests of No Differences Among Time Points

If the parallelism hypothesis is reasonable, the test for differences among time points can be carried out using the sum (or average) across groups of the observations at each time point. This test of H_{02} is equivalent to a one – sample T^2-test.

In this case null hypothesis is: H_{03} : ABC = D

where $A_{1\times s}$ = (1,……..,1) or (1/s,……..,1/s)

$$C_{t\times(t-1)} = \begin{pmatrix} I_{t-1} \\ -1'_{t-1} \end{pmatrix}$$

$$D_{(s-1)\times t} = 0'_{t-1}$$

This procedure weights each of the s groups equally and is usually appropriate. However, if unequal group sizes result from the nature of the experimental conditions, it may desirable to use a weighted average rather than a simple average. In this case $A=(n_1, n_{2,\ldots,} n_s)$ or $A=(1/n).(n_1, n_{2,\ldots,} n_s)$ can be used, C and D being unchanged.

The hypothesis H_{03} can also be tested without assuming parallelism:

$$H_{02} : \begin{pmatrix} \mu_{11} \\ \mu_{12} \\ . \\ \mu_{1t} \end{pmatrix} = \begin{pmatrix} \mu_{12} \\ \mu_{22} \\ . \\ \mu_{s2} \end{pmatrix} = \ldots\ldots\ldots = \begin{pmatrix} \mu_{1t} \\ \mu_{2t} \\ . \\ \mu_{st} \end{pmatrix}$$

In this case,

$$A_{s\times s} = I_s$$

$$C_{t\times t-1} = \begin{pmatrix} I_{t-1} \\ -1'_{t-1} \end{pmatrix}$$

$$D_{s\times t-1} = \begin{pmatrix} 0\ldots\ldots\ldots 0 \\ . \quad\quad . \\ 0\ldots\ldots\ldots 0 \end{pmatrix}$$

If comparisons among time points in a particular group (or subset of groups) are of interest, the rows of a corresponding to the excluded groups can be omitted.

2.3 Nonparametric Methods

Here we have used two nonparametric tests for analysis of the data:

(1) Multivariate multisample rank sum test
(2) Multivariate multisample median test

2.3.1 Multivariate Multisample Rank Sum Test

For each sample at each time point, the multivariate multisample rank sum test (MMRST) compares the difference between the sample average rank and the combined-data average rank. Let $\mathbf{r_h}$ denote the t×1 vector of average ranks from group h, with elements $r_{hj} = \sum_{i=1}^{n_h} \frac{r_{hij}}{n_h}$, where r_{hij} is the rank of the j[th] response from the i[th] subject in sample h. Let $\bar{r}.$ denote the average rank vector (t×1) for the combined samples;

the j[th] component of $\bar{r}.$ is

$$\bar{r}._{\mathrm{j}} = \frac{\sum_{h=1}^{s}\sum_{i=1}^{n_h} r_{hij}}{\sum_{h=1}^{s} n_h} \tag{7}$$

The test statistic is

$$L_{RS} = \sum_{h=1}^{s} n_h (r_h - \bar{r}.)' V^{-1} (r_h - \bar{r}.), \tag{8}$$

where the covariance matrix V has elements

$$V_{jl} = \left(\sum_{h=1}^{s}\sum_{i=1}^{n_h} r_{hij} r_{hil} \Big/ \sum_{h=1}^{s} n_h \right) - \bar{r}._j \bar{r}._l \tag{9}$$

The statistic L_{RS} tests the hypothesis of no differences in the multivariate response profiles from the s samples, the asymptotic null distribution of this statistic is $\chi^2_{t(s-1)}$.

2.4 Multivariate multisample median test

For each sample at each time point, the multivariate multisample median test (MMMT) compares difference between proportions of responses less than or equal to the median to the corresponding combined-data proportions. Let p_h denote the t×1 vector of proportions from the h[th] sample that are less than or equal to the median of the combined samples. The j[th] component of p_h is

$$p_{hj} = \sum_{i=1}^{n_h} x_{hij} \Big/ n_h ,$$

where

$$x_{hij} = \begin{cases} 1 & \text{if rhij} \le \sum_{h=1}^{s} n_h / 2 \\ 0 & otherwise \end{cases} \quad (10)$$

Let $\overline{p}_{\cdot}$ denote the t×1 vector of proportions of observations from the combined samples that are less than or equal to the median of the combined samples, with elements

$$\overline{p}_{\cdot j} = \frac{\sum_{h=1}^{s}\sum_{i=1}^{n_h} x_{hij}}{\sum_{h=1}^{s} n_h} \quad (11)$$

The test statistic is

$$L_M = \sum_{h=1}^{s} n_h (p_h - \overline{p}_{\cdot})' V^{-1} (p_h - \overline{P}_{\cdot}) \quad (12)$$

where the covariance matrix V has elements

$$V_{jl} = \left(\sum_{h=1}^{s}\sum_{i=1}^{n_h} x_{hij} x_{hil} \Big/ \sum_{h=1}^{s} n_h \right) - \overline{p}_{\cdot j}\, \overline{p}_{\cdot l} \quad (13)$$

The statistic L_M tests the hypothesis of no differences in the multivariate response profiles from the s samples. The asymptotic null distribution of L_M is $\chi^2_{t(s-1)}$. If t=1, L_M reduces to the several-sample median test.

2.5 Data Used

In the present study, we have used data due to Grizzel and Allen (1969) published in Davis (2002). The data are related to the measurement of coronary sinus potassium (MIL equivalents per liter) from four groups of dogs. Group 1 was a control group of 9 untreated dogs with coronary occlusion. The 10 animals in group 2 were given extrinsic cardiac denervation three weeks prior to coronary occlusion, whereas the 8 animals in group 3 were similarly treated immediately prior to coronary occlusion. Group 4 consisted of 9 dogs treated with bilateral thoracic sympathectomy and stellectomy three weeks prior to coronary occlusion. The data are shown in Table-2.

Group	**Dog**	**Minutes after occlusion**						
		1	**3**	**5**	**7**	**9**	**11**	**13**
1	1	4.0	4.0	4.1	3.6	3.6	3.8	3.1

	2	4.2	4.3	3.7	3.7	4.8	5.0	5.2
	3	4.3	4.2	4.3	4.3	4.5	5.8	5.4
	4	4.2	4.4	4.6	4.9	5.3	5.6	4.9
	5	4.6	4.4	0.3	5.6	5.9	5.9	5.3
	6	3.1	3.6	4.9	5.2	5.3	4.2	4.1
	7	3.7	3.9	3.9	4.8	5.2	5.4	4.2
	8	4.3	4.2	4.4	5.2	5.6	5.4	4.7
	9	4.6	4.6	4.4	4.6	5.4	0.9	5.6
2	10	3.4	3.4	3.5	3.1	3.1	3.7	3.3
	11	3.0	3.2	3.0	3.0	3.1	3.2	3.1
	12	3.0	3.1	3.2	3.0	3.3	3.0	3.0
	13	3.1	3.2	3.2	3.2	3.3	3.1	3.1
	14	3.8	3.9	4.0	2.9	3.5	3.5	3.4
	15	3.0	3.6	3.2	3.1	3.0	3.0	3.0
	16	3.3	3.3	3.3	3.4	3.6	3.1	3.1
	17	4.2	4.0	4.2	4.1	4.2	4.0	4.0
	18	4.1	4.2	4.3	4.3	4.2	4.0	4.2
	19	4.5	4.4	4.3	4.5	5.3	4.4	4.4
3	20	3.2	3.3	3.8	3.8	4.4	4.2	3.7
	21	3.3	3.4	3.4	3.7	3.7	3.6	3.7
	22	3.1	3.3	3.2	3.1	3.2	3.1	3.1
	23	3.6	3.4	3.5	4.6	4.9	5.2	4.4
	24	4.0	4.5	5.4	5.7	4.9	4.0	4.0
	25	3.7	4.0	4.4	4.2	4.6	4.8	5.4
	26	3.5	3.9	0.8	5.1	4.9	5.3	5.6
	27	3.9	4.0	4.1	5.0	5.4	4.4	3.9
4	28	3.1	3.5	3.5	3.2	3.0	3.0	3.2
	29	3.3	3.2	3.6	3.7	3.7	4.2	4.4
	30	3.5	3.9	4.7	4.3	3.9	3.4	3.5
	31	3.4	3.4	3.5	3.3	3.4	3.2	3.4
	32	3.7	3.8	4.2	4.3	3.6	3.8	3.7
	33	4.0	3.6	4.8	4.9	5.4	5.6	4.8
	34	4.2	3.9	4.5	4.7	3.9	3.8	3.7
	35	4.1	4.1	3.7	4.0	4.1	4.6	4.7
	36	3.5	3.6	3.6	4.2	4.8	4.9	5.0

Table 2: Measurement of coronary sinus potassium from four groups of dogs

3. STATISTICAL ANALYSIS OF DATA

3.1 Multivariate Analysis of Variance (MANOVA)

In this section, we have carried out MANOVA for the data due to Grizzle and Allen (1969). All the results are obtained by using SAS System with the GLM Procedure and are given below:

Class Level Information for Dataset 1

Class: Group Levels: 4
Values: 1 2 3 4 Number of Observations Read: 36
Number of Observations Used: 36

Source	d.f.	S.S.	M.S.	F value	Pr>F
Model	3	2.01363889	0.67121296	3.28	0.0335
Error	32	6.55386111	0.20480816		
Corrected Total	35	8.56750000			

Table 3: ANOVA Table (Dependent Variable: min1 min1)

Source	d.f.	S.S.	M.S.	F value	Pr>F
Model	3	1.77816667	0.59272222	4.06	0.0149
Error	32	4.67155556	0.14598611		
Corrected Total	35	6.44972222			

Table 4: ANOVA Table ((Dependent Variable: min 3 min 3)

Source	d.f.	S.S.	M.S.	F value	Pr>F
Model	3	1.10094444	0.36698148	0.37	0.7785
Error	32	32.14211111	1.00444097		
Corrected Total	35	33.24305556			

Table 5: ANOVA Table (Dependent Variable: min 5 min 5)

Source	d.f.	S.S.	M.S.	F value	Pr>F
Model	3	7.59016667	2.53005556	5.45	0.0038
Error	32	14.84655555	0.46394444		
Corrected Total	35	22.43638889			

Table 6: ANOVA Table (Dependent Variable: min 7 min 7)

Source	d.f.	S.S.	M.S.	F value	Pr>F
Model	3	10.62266667	3.54088889	6.97	0.0010
Error	32	16.25955556	0.50811111		
Corrected Total	35	26.88222222			

Table 7: ANOVA Table (Dependent Variable: min 9 min 9)

Source	d.f.	S.S.	M.S.	F value	Pr>F
Model	3	6.90583333	2.30194444	2.29	0.0974
Error	32	32.19722222	1.00616319		
Corrected Total	35	39.10305556			

Table 8: ANOVA Table (Dependent Variable: min 11 min 11)

Source	d.f.	S.S.	M.S.	F value	Pr>F
Model	3	7.73072222	2.57690741	4.95	0.0062
Error	32	16.65677778	0.52052431		
Corrected Total	35	24.38750000			

Table 9: ANOVA Table (Dependent Variable: min 13 min 13)

Repeated Measures Level Information

Dependent variable : min1 min3 min5 min7 min9 min11 min13

Level of min : 1 2 3 4 5 6 7

MANOVA test criteria and exact F statistics for hypothesis of no min effect

H = Type III SSCP matrix for min; E = error SSCP matrix

S=1 M=2 N=12.5

Statistic	Value	F value	Num DF	Den DF	Pr>F
Wilks' Lambda	0.41572789	6.32	6	27	0.003
Pillai's Trace	0.58427211	6.32	6	27	0.003
Hotelling-Lawley Trace	1.40541957	6.32	6	27	0.003
Roy's Greatest Root	1.40541957	6.32	6	27	0.003

Table 10: Test statistics for the hypothesis of no min effect

MANOVA test criteria and F statistics for hypothesis of no min*group effect

H = Type III SSCP matrix for min*group; E = Error SSCP matrix

S=3 M=1 N=12.5

Statistic	Value	F value	Num DF	Den DF	Pr>F
Wilks' Lambda	0.38024086	1.74	18	76.853	0.0499
Pillai's Trace	0.78796529	1.72	18	87	0.0503
Hotelling-Lawley Trace	1.20860876	1.75	18	48.296	0.0621
Roys's Greatest Root	0.60065695	2.90	6	29	0.0243

Table 11: Test statistics for the hypothesis of no min*group effects

Statistic	Value	F value	Num DF	Den DF	Pr>F
Wilks' Lambda	0.74974530	6.79	3	61	0.0005
Pillai's Trace	0.25025470	6.79	3	61	0.0005
Hotelling-Lawley Trace	0.33378630	6.79	3	61	0.0005
Roys's Greatest Root	0.33378630	6.79	3	61	0.0005

Table 12: Test statistics for the hypothesis of no group effects

ANOVA was carried out by using SAS first at different time points separately. Tables 3, 4, 6, 7 and 9 reveal that Pr>F corresponding to time points minute 1, 3, 7, 9, and 13 respectively are 0.0335, 0.0149, 0.0038, 0.0010 and 0.0062 each one of which is less than 0.05 (level of significance), hence it is concluded that different groups of dogs differ significantly at 1, 3, 7, 9, and 13 time points with respect to coronary sinus potassium. Whereas Tables 3 and 6 reveal that Pr>F corresponding to time points 5 and 11 respectively are 0.7785 and 0.0974 which are greater than 0.05 (level of significance), hence coronary sinus potassium does not differ significantly among four groups of dogs at time points 5 and 11.

The values of 4 test statistics viz. Wilk's Lambda, Pillai's Trace, Hotelling-Lawley Trace and Roy's Greatest Root were calculated under MANOVA corresponding to time (min) effect, time*group effect and group effect by using SAS, whose values along with the corresponding p-values (Pr>F) are shown in Tables 10, 11 and 12 respectively. Table 11 reveals significant values of Wilk's Lambda and Roy's greatest root statistics (Pr>F=0.0499 & 0.0243 respectively) and insignificant values (Pr>F=0.0503 & 0.0621 respectively) of Pillai's Trace, Hotelling-Lawley for time*group effect, hence time*effect may be considered significant under Wilk's Lambda and Roy's greatest root statistics and insignificant under Pillai's Trace and Hotelling-Lawley Trace statistics. Table 10 reveals that time (min) effect is significant (Pr>F=0.003 for all the 4 test statistics). Moreover, group effects are also significant (Pr>F=0.0005 for all the 4 test statistics) as revealed by Table 12 Therefore, it is concluded that different groups of dogs differ significantly with respect to coronary sinus potassium.

3.2 Profile Analysis

In this section, we have carried out Profile analysis of the data due to Grizzle and Allen (1969), described in previous section. For testing H_{01} (i.e. testing for parallelism), we generate a new observation table by computing (t-1) differences between adjacent time points from each sampling unit from original observation table as shown in Table 13.

Group	Dog	Differences between adjacent time points					
		(t_1-t_2)	(t_2-t_3)	(t_3-t_4)	(t_4-t_5)	(t_5-t_6)	(t_6-t_7)
1	1	0	-0.1	0.5	0	-0.2	0.7
	2	-0.1	0.6	0	-1.1	-0.2	-0.2
	3	0.1	-0.1	0	-0.2	-1.3	0.4
	4	-0.2	-0.2	-0.3	-0.4	-0.3	0.7
	5	0.2	-0.9	-0.3	-0.3	0	0.6
	6	-0.5	-1.3	-0.3	-0.1	1.1	0.1
	7	-0.2	0	-0.9	-0.4	-0.2	1.2
	8	0.0	-0.2	-0.8	-0.4	0.2	0.7
	9	0	0.2	-0.2	-0.8	-0.5	0.3
2	10	0	-0.1	0.4	0	-0.6	0.4
	11	-0.2	0.2	0	-0.1	-0.1	0.1
	12	-0.1	-0.1	0.2	-0.3	0.3	0
	13	-0.1	0	0	-0.1	0.2	0
	14	-0.1	-0.1	1.1	-0.6	0	0.1
	15	-0.6	0.4	0.1	0.1	0	0
	16	0	0	-0.1	-0.2	0.5	0
	17	0.2	-0.2	0.1	-0.1	0.2	0
	18	-0.1	-0.1	0	0.1	0.2	-0.2
	19	0.1	0.1	-0.2	-0.8	0.5	0
3	20	-0.1	-0.5	0	-0.6	0.2	0.5
	21	-0.1	0	-0.3	0	0.1	-0.1
	22	-0.2	0.1	0.1	-0.1	0.1	0
	23	0.2	-0.1	-1.1	-0.3	-0.3	0.8
	24	0	-0.9	-0.3	0.8	0.9	0
	25	-0.3	-0.4	0.2	-0.4	-0.2	-0.6
	26	-0.4	-1.9	0.4	0.5	-0.4	-0.3
	27	-0.1	-0.1	-0.9	-0.4	1	0.5
4	28	-0.4	0	0.3	0.2	0	-0.2
	29	0.1	-0.4	-0.1	0	1.5	-2.2
	30	-0.4	-0.8	0.4	0.4	0.5	-0.1
	31	0	-0.1	0.2	-0.1	0.2	-0.2
	32	-0.1	-0.4	-0.1	0.7	-0.2	0.1
	33	-0.6	-0.2	-0.1	-0.5	-0.2	0.8
	34	0.3	-0.6	-0.2	0.8	0.1	0.1
	35	0	0.4	-0.3	-0.1	-0.5	-0.1
	36	-0.1	0	-0.6	-0.6	-0.1	-0.1

Table 13: Differences between adjacent time points

Let $\bar{y}_1$, $\bar{y}_2$, $\bar{y}_3$ and $\bar{y}_4$ denote the four mean vectors corresponding to four groups of the new observation table and $\bar{y}$ denotes the overall mean vector, then

$$\bar{y}^{1} = \begin{pmatrix} -0.07 \\ -0.22 \\ -0.26 \\ -0.41 \\ -0.16 \\ +0.5 \end{pmatrix}, \quad \bar{y}^{2} = \begin{pmatrix} -0.09 \\ +0.01 \\ +0.16 \\ -0.2 \\ +0.12 \\ +0.04 \end{pmatrix}, \quad \bar{y}^{3} = \begin{pmatrix} -0.125 \\ -0.475 \\ -0.238 \\ -0.063 \\ +0.175 \\ +0.1 \end{pmatrix}, \bar{y}^{4} = \begin{pmatrix} -0.133 \\ -0.233 \\ -0.056 \\ +0.088 \\ +0.144 \\ -0.211 \end{pmatrix}, \bar{y} = \begin{pmatrix} -0.103 \\ -0.215 \\ -0.087 \\ -0.150 \\ +0.068 \\ +0.105 \end{pmatrix}$$

As profile analysis is equivalent to MANOVA on the (t-1) differences between adjacent time points from each sampling unit, we have calculated matrices W and Q.

Here, the determinant values of W and (W+Q) are

|W|=8415.102, |W+Q|=22435.89

and Wilks' lambda $\Lambda = 0.375$

Bartlett's χ^2-statistic=12.777 and $\chi^2_{63,0.05} = 82.52873$

Since $\chi^2 < \chi^2_{63,0.05}$ therefore H_{01} is accepted, hence, the profiles for all the four groups are parallel.

For testing H_{02}, we have considered total across time from each subject from the given original data (Table 2) and have carried out one-way ANOVA. The summary of calculations is given below:

(1) Total sum of square (TSS) = 698.09
(2) Between sum of square (BSS) = 274.38
(3) Error sum of square (ESS) = 423.71

One-way-ANOVA is shown in Table 14.

Source of variations	DF	SS	MSS	F value
Between groups	3	274.38	91.46	6.9078
Error	32	423.71	13.24	
Total	35			

Table 14: ANOVA Table for total across time from each subject

Here, $F_{(3,32,0.05)} = 2.90112$, which is smaller than F_{cal}, therefore H_{02} is rejected and we conclude that there is a significant difference among groups i.e. dogs of different groups differ significantly with respect to coronary sinus potassium.

For testing H_{03}, again we generated a new observation table using weighted average of the observations across groups (which are of unequal sizes) at each time point from the given original data and calculated means corresponding to seven time points of the new observation table as given below:

Let y_{ij} denote the response from the subject i at time j, where i=1,2,…..,10 and j=1,2,…..,7, and $\bar{y}^{1}$, $\bar{y}^{2}$, $\bar{y}^{3}$, $\bar{y}^{4}$, $\bar{y}^{5}$, $\bar{y}^{6}$ $\bar{y}^{7}$ denote the mean corresponding to seven time points of the new observation table and the values are

$\bar{y}^{1}$ =3.785, $\bar{y}^{2}$ =3.87, $\bar{y}^{3}$ =4.046, $\bar{y}^{4}$ =4.135, $\bar{y}^{5}$ =4.341, $\bar{y}^{6}$ =4.256, $\bar{y}^{7}$ =4.111

Next, we generated another table from the abovesaid Table, by computing (t-1) differences between adjacent time points from each sampling unit and made the following calculations:

Let $Y^{*}_{ij} = y_{ij} - y_{i(j+1)}$ denote the response from subject i at time j, where i=1,2,…..,10 and j=1,2,….,6 and $Y^{*}_{i} = (Y^{*}_{i1}, Y^{*}_{i2}, \ldots\ldots, Y^{*}_{i,t-1})'$ are the vectors of the sample. Let $\bar{Y}^{*}$ denote the mean vector over subjects, then.

$$\bar{Y}^{*} = \begin{pmatrix} -0.085 \\ -0.176 \\ -0.089 \\ -0.206 \\ +0.085 \\ +0.145 \end{pmatrix}$$

Test statistic is defined by $F = \dfrac{(n-p+1)}{(p-1)} \dfrac{T^2}{n}$

Where $T^2 = n\ \bar{Y}^{*'} (S^{*})^{-1}\ \bar{Y}^{*}$; $\quad S^{*} = \dfrac{1}{n-1} \sum_{i=1}^{n} (Y^{*}_{i} - \bar{Y}^{*})(Y^{*}_{i} - \bar{Y}^{*})'$,

Here, T^2=344.5651, F=45.9420, and $F_{(6,30,0.05)}$=2.4205.

Since $F > F_{(6,30,0.05)}$, therefore H_{03} is rejected i.e. there is a significant difference among time points. Hence, we conclude that different groups of dogs differ significantly with respect to coronary sinus potassium at all time points.

3.3 Non-Parametric Multivariate Multisample Rank Sum Test

In this section, we have analyzed the data by using multivariate multisample rank sum test (MMRST). Let r_1, r_2, r_3, r_4 are the vectors of average ranks corresponding

to the four groups of data, and $\bar{r}_.$ denote the average rank vector for the combined groups

$$r_1 = \begin{pmatrix} 19.33 \\ 19.89 \\ 26.39 \\ 33 \\ 43.44 \\ 46.56 \\ 35.39 \end{pmatrix}, r_2 = \begin{pmatrix} 33.95 \\ 41.2 \\ 39.9 \\ 30.25 \\ 38.35 \\ 33.3 \\ 31.55 \end{pmatrix}, r_3 = \begin{pmatrix} 16.75 \\ 20.81 \\ 29 \\ 34.31 \\ 36.31 \\ 32.31 \\ 30 \end{pmatrix}, r_4 = \begin{pmatrix} 23.33 \\ 28.11 \\ 34.78 \\ 37 \\ 32.72 \\ 33.5 \\ 34.56 \end{pmatrix}, \bar{r}_. = \begin{pmatrix} 98.11 \\ 110.81 \\ 129.25 \\ 134.07 \\ 144.75 \\ 139.71 \\ 128.81 \end{pmatrix}$$

from which we obtained the covariance matrix V and then the value of test statistic L_{RS}.

Here; Test statistic L_{RS}=13.530742

$$\chi^2_{21,0.05} = 32.67$$

Since $L_{RS} < \chi^2_{21,0.05}$; hence H_{01} is accepted i.e. there are no significant differences in the multivariate response profiles from all groups.

3.4 Non-Parametric Multivariate Multisample Median Test

Now we analyze the same data by multivariate multisample median test. Let p_1, p_2, p_3, p_4 be the vectors of proportions corresponding to the four groups of data, and $\bar{p}_.$ denote the vector of proportions of observations from the combined groups;

$$p_1 = \begin{pmatrix} 4.111 \\ 4.177 \\ 4.4 \\ 4.655 \\ 5.066 \\ 5.222 \\ 4.722 \end{pmatrix}, p_2 = \begin{pmatrix} 3.54 \\ 3.63 \\ 3.62 \\ 3.46 \\ 3.66 \\ 3.50 \\ 3.46 \end{pmatrix}, p_3 = \begin{pmatrix} 3.6 \\ 3.725 \\ 4.2 \\ 4.437 \\ 4.5 \\ 4.325 \\ 4.225 \end{pmatrix}, p_4 = \begin{pmatrix} 3.644 \\ 3.777 \\ 4.011 \\ 4.066 \\ 3.977 \\ 3.833 \\ 4.044 \end{pmatrix}, \bar{p}_. = \begin{pmatrix} 3.722 \\ 3.825 \\ 4.042 \\ 4.127 \\ 4.277 \\ 4.197 \\ 4.091 \end{pmatrix}$$

from which we obtained the covariance matrix V and then the value of test statistic L_M.

Here; Test statistic L_M=2.698953

$$\chi^2_{21,0.05} = 32.67057$$

Since $L_M < \chi^2_{t(s-1)}$; hence H_{01} is accepted i.e. there are no significant differences in the multivariate response profiles from all groups.

4. Comparison of Different Methods of Analysis

Four different methods were used for the analysis of data described earlier. The method of MANOVA led to the conclusion that different groups of dogs differ significantly with respect to coronary sinus potassium. The findings coincided for all the four test statistics (Wilk's Lambda, Pillai's Trace, Hotelling-Lowley Trace and Roy's largest root statistics). Time effects were also found significant for all the test statistics, whereas time*group effects were found significant under Wilk's Lambda and Roy's largest root statistic and insignificant under Pillai's trace and Hotelling-Lowley's trace statistics.

Profile analysis was applied to the said data to find whether the hypothesis of parallelism is satisfied and time as well as group effects are significant or not. The findings reveal that the hypothesis of parallelism is satisfied but the group effects are significant. Moreover, time effects were also found significant. Thus, profile analysis led to similar results as revealed by MANOVA.

Lastly, multivariate non-parametric methods (Multivariate multisample rank sum test and multivariate multisample median test) were applied to the said data and led to the conclusion that multivariate response profiles from different groups are insignificant. This conclusion is some what different from the conclusions of MANOVA and profile analysis. This is probably due to the fact that under the former methods, we have assumed normality of the population whereas in non-parametric methods such assumption is not necessary.

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