Ann. Inst. Statist. Math.
Vol. 40, No. 1, 179–186 (1988)

SCORE AND WALD TESTS FOR THE MULTIVARIATE GROWTH CURVE MODEL WITH MISSING DATA

KAO-TAI TSAI[1] AND JAMES A. KOZIOL[2]

[1]*AT&T Bell Laboratories, Murray Hill, New Jersey, U.S.A.*
[2]*Research Institute of Scripps Clinic, La Jolla, California, U.S.A.*

(Received March 3, 1986; revised February 16, 1987)

Abstract. We present the score and Wald test analogues to Srivastava's (1985, *Comm. Statist. A—Theory Methods*, **14**, 775–792) likelihood ratio tests for the multivariate growth curve model with missing data, and illustrate their use with data from an immunotherapy experiment (Fukushima *et al.* (1982, *Int. J. Cancer*, **29**, 107–112, 113–117)).

Key words and phrases: Potthoff-Roy model, multivariate regression, score, Wald and likelihood ratio tests.

1. Introduction

Potthoff and Roy (1964) introduced a generalization of the usual multivariate analysis of variance model, and showed that their generalized model is pertinent to polynomial growth curve analyses. Rao (1965, 1966) and Khatri (1966) further developed the Potthoff-Roy growth curve model, deriving appropriate likelihood ratio test procedures and confidence intervals for the unknown model parameters. Kleinbaum (1973) considered a further extension of the growth curve model to incorporate missing data problems, and proposed in these situations asymptotic Wald tests for parameter values based on best asymptotically normal estimators. However, various difficulties attend Kleinbaum's procedures: his estimated covariance matrices may not necessarily be positive definite in small samples; and, Schwertman (1974) and later Leeper and Woolson (1982) reported that his procedures can be profoundly anticonservative, simulated significance levels being much too large with small data sets. Recently, Srivastava (1985) explicitly derived likelihood ratio tests for Kleinbaum's growth curve problem with missing data. Our aim in this note is to present an alternative development to that of Srivastava: in particular, we shall provide the score and Wald tests analogues to his likelihood ratio tests. These procedures complement Srivastava's approach, and may be computationally more attractive. Section 2 contains

preliminaries to the delineation of the test statistics in Section 3. We illustrate these procedures with an example in Section 4.

2. The multivariate growth curve model with missing data: Notational conventions

Let

$$Y = C\xi A + E ,$$

where $Y: p\times n$ is the observation matrix of n independent $p\times 1$ vectors, $C: p\times q$ is of rank $q\leq p$, $\xi: q\times m$ is the matrix of unknown parameters, $A: m\times n$ is of rank $m<n$, and the n columns of E are independently distributed as $N_p(0, \Sigma)$. Following Srivastava (1985), when the data matrix Y contains missing values, we partition it into k distinct blocks ($1\leq k\leq 2^p-1$) of independent subsets $Y_{(1)}$, $Y_{(2)},\ldots, Y_{(k)}$, the i-th subset consisting of the $n_i>0$ independent observations evincing the same pattern of missing values. We then partition A and E accordingly, and write

$$\begin{aligned} Y_{p\times n} &= (Y_{\underset{p\times n_1}{(1)}}, Y_{\underset{p\times n_2}{(2)}},\ldots, Y_{\underset{p\times n_k}{(k)}}) \\ &= C\,\xi\,(A_{\underset{m\times n_1}{1}}, A_{\underset{m\times n_2}{2}},\ldots, A_{\underset{m\times n_k}{k}}) + (E_{\underset{p\times n_1}{1}}, E_{\underset{p\times n_2}{2}},\ldots, E_{\underset{p\times n_k}{k}}) . \end{aligned}$$

Introduce the $p_i\times p$ incidence matrices B_i, $1\leq i\leq k$, each consisting of ones and zeros such that the transformation

$$Z_i = B_i Y_{(i)} ,$$

recovers all the observed data in the i-th block $Y_{(i)}$. Then

$$Z_i = B_i C\xi A_i + B_i E_i ,$$

and the covariance matrix of the n_i independent column vectors of Z_i is

$$U_i = B_i \Sigma B_i' .$$

Lastly, we may now write the log likelihood function for our data as

$$\log L = \text{const.} - \sum_{i=1}^{k} \frac{n_i}{2} \log |U_i| - \frac{1}{2} \sum_{i=1}^{k} \operatorname{tr} U_i^{-1} P_i P_i' ,$$

where

$$P_i = Z_i - B_i C\xi A_i .$$

3. Derivation of the test statistics

We may now proceed with the derivation of the score and Wald tests. (In the following, our notation for differentiation with vectors and matrices is that of Dwyer (1967)).

We introduce the information matrix $I(\xi, \Sigma)$:

$$I(\xi, \Sigma) = \begin{pmatrix} \frac{\partial}{\partial \xi_r} \frac{\partial \log L}{\partial \xi_r} & \frac{\partial}{\partial \Sigma_r} \frac{\partial \log L}{\partial \xi_r} \\ \frac{\partial}{\partial \xi_r} \frac{\partial \log L}{\partial \Sigma_r} & \frac{\partial}{\partial \Sigma_r} \frac{\partial \log L}{\partial \Sigma_r} \end{pmatrix}$$

$$\stackrel{\text{def}}{=} \begin{pmatrix} I_{\xi\xi}(\xi, \Sigma) & I_{\xi\Sigma}(\xi, \Sigma) \\ I_{\Sigma\xi}(\xi, \Sigma) & I_{\Sigma\Sigma}(\xi, \Sigma) \end{pmatrix}.$$

In this regard, we may show that

$$I_{\xi\xi}(\xi, \Sigma) = \sum_{i=1}^{k} - (C'B_i'U_i^{-1}B_iC) \otimes (A_iA_i') , \tag{3.1}$$

$$I_{\xi\Sigma}(\xi, \Sigma) = \sum_{i=1}^{k} (C'B_i'U_i^{-1}B_i)' \otimes (B_i'U_i^{-1}P_iA_i') , \tag{3.2}$$

$$\begin{aligned} I_{\Sigma\xi}(\xi, \Sigma) = &- \frac{1}{2} \sum_{i=1}^{k} (B_i'U_i^{-1}B_iC)' \otimes (A_iP_i'U_i^{-1}B_i) \\ &+ (B_i'U_i^{-1}P_iA_i')' \otimes (C'B_i'U_i^{-1}B_i) , \end{aligned} \tag{3.3}$$

and

$$\begin{aligned} I_{\Sigma\Sigma}(\xi, \Sigma) = &\sum_{i=1}^{k} \frac{n_i}{2} (B_i'U_i^{-1}B_i) \otimes (B_i'U_i^{-1}B_i) \\ &- \frac{1}{2} \sum_{i=1}^{k} (B_i'U_i^{-1}B_i) \otimes (B_i'U_i^{-1}P_iP_i'U_i^{-1}B_i) \\ &- \frac{1}{2} \sum_{i=1}^{k} (B_i'U_i^{-1}P_iP_i'U_i^{-1}B_i) \otimes (B_i'U_i^{-1}B_i) . \end{aligned} \tag{3.4}$$

The calculations leading to (3.1)–(3.4) are straightforward, along the lines given in Srivastava (1985), but are somewhat tedious; hence, details are regulated to a technical report available from the authors.

Upon taking expectations, certain simplifications arise:

$$E[I_{\xi\Sigma}(\xi, \Sigma)] = 0 ,$$

$$E[I_{\Sigma\xi}(\xi, \Sigma)] = 0 ,$$

and

$$E[I_{\Sigma\Sigma}(\xi, \Sigma)] = -\sum_{i=1}^{k} \frac{n_i}{2} (B_i' U_i^{-1} B_i) \otimes (B_i' U_i^{-1} B_i) .$$

Nevertheless, the information matrix $I(\xi, \Sigma)$ depends on unknown parameters, consistent estimates of which can be used without affecting distributional results. Thus, let $\hat{\xi}$ and $\hat{\Sigma}$ denote the solutions of the systems of equations for the complete model:

$$\frac{\partial \log L}{\partial \xi} = 0 ,$$

$$\frac{\partial \log L}{\partial \Sigma} = 0 .$$

We may now describe the Wald and score test statistics in a straightforward manner. Let

$$i(\theta) = i(\xi, \Sigma) = -E[I(\xi, \Sigma)] .$$

Then (Cox and Hinkley (1974)), the Wald statistic for the general null hypothesis H_0: $\theta \in \Omega_0$, where Ω_0 is a specified subspace of the general parameter space Ω, is

$$W_e = (\hat{\theta} - \hat{\theta}_0)' \, i(\hat{\theta}) \, (\hat{\theta} - \hat{\theta}_0) .$$

In particular, the Wald statistic for H_0: $\xi \in \Xi_0$ is

$$W_e = (\hat{\xi} - \hat{\xi}_0)' \, i(\hat{\xi}, \hat{\Sigma}) \, (\hat{\xi} - \hat{\xi}_0) .$$

Since $\hat{\xi}$ and $\hat{\Sigma}$ are the maximum likelihood estimates of ξ and Σ respectively under the full model, we have

$$\begin{aligned} i(\hat{\xi}, \hat{\Sigma}) &= i_{\xi\xi}(\hat{\xi}, \hat{\Sigma}) - i_{\xi\Sigma}(\hat{\xi}, \hat{\Sigma}) \, i_{\Sigma\Sigma}^{-1} \, (\hat{\xi}, \hat{\Sigma}) \, i_{\xi\Sigma}'(\hat{\xi}, \hat{\Sigma}) \\ &= \sum_{i=1}^{k} (C' B_i' \hat{U}_i^{-1} B_i C) \otimes (A_i A_i') . \end{aligned}$$

Therefore,

$$W_e = (\hat{\xi} - \xi_0)' \sum_{i=1}^{k} (C'B_i'\hat{U}_i^{-1}B_iC) \otimes (A_iA_i') \cdot (\hat{\xi} - \xi_0) .$$

Similarly, let

$$U_\xi(\xi, \Sigma) = \frac{\partial \log L}{\partial \xi} = \sum_{i=1}^{k} C'B_i'U_i^{-1}P_iA_i' .$$

Then, the score test W_u for the null hypothesis H_0: $\xi \in \Xi_0$ is

$$W_u = U_\xi'(\hat{\xi}_0, \hat{\Sigma}_0)\, i^{\xi\xi}\, (\hat{\xi}_0, \hat{\Sigma}_0)\, U_\xi\, (\hat{\xi}_0, \hat{\Sigma}_0) ,$$

where

$$i^{\xi\xi} = i_{\xi\xi}^{-1} + i_{\xi\xi}^{-1}\, i_{\xi\Sigma}(i_{\Sigma\Sigma} - i_{\Sigma\xi}\, i_{\xi\xi}^{-1}\, i_{\xi\Sigma})^{-1}\, i_{\Sigma\xi}\, i_{\xi\xi}^{-1} .$$

Under rather general conditions (Sundberg (1974)), the score and Wald tests are asymptotically equivalent under the null hypothesis, and are asymptotically distributed as chi-squared random variables with degrees of freedom equalling the difference in the dimensions of the parameter space under the full and the null model.

4. An example

A series of immunotherapy experiments was recently undertaken to investigate whether a combination of syngeneic normal spleen cells, xenogeneic immune RNA, and other tumor antigen, injected subcutaneously at the sites of induced CT26 (colon carcinoma) tumors in a homogeneous population of BALB/c mice, would lead to significantly smaller tumor growth and enhanced survival compared with mice not receiving injections of this ternary immunotherapy regimen. These experiments and their implications are discussed in detail by Fukushima *et al.* (1982*a*, 1982*b*). Here we focus on one experiment, in which 30 BALB/c mice with induced CT26 tumors were randomly divided into three groups of 10 mice each, and subjected to different immunotherapy regimens: Group 1 received injections of tissue culture medium around the growing tumors; Group 2 received injections of tissue culture medium and normal spleen cells; and Group 3 received injections of normal spleen cells, immune RNA and tumor antigen. The relevant data are presented in Table 1. In Fig. 1, where mean tumor size in each group is plotted against time, there is some indication that Group 3 had consistently smaller tumor sizes than the other groups. Nevertheless, we cannot reject the hypothesis of equality of tumor size across time among the three groups with either the score test or the Wald test: we find that W_u=4.932 and W_e=5.359, each statistic approximately chi-squared with 22 degrees of freedom. In

Table 1. Tumor sizes (mm^3) over the course of the experiment.

	Day										
	7	11	12	13	14	15	17	18	19	20	21
Group 1	29.8	157.0	126.8	202.5	225.0	307.2	320.1	NA	NA	NA	NA
	70.0	129.7	196.0	205.8	375.7	419.1	421.2	573.4	701.8	NA	NA
	35.3	157.1	122.5	217.6	340.3	379.0	556.6	661.3	634.8	NA	NA
	27.0	122.4	196.1	196.1	332.2	388.9	469.3	397.1	505.4	541.5	NA
	24.6	168.8	135.3	196.0	340.2	340.4	507.3	767.2	820.0	937.5	NA
	55.0	95.0	205.9	205.9	270.0	307.3	405.1	726.0	950.4	661.5	798.6
	19.6	152.2	129.6	176.6	213.9	317.9	356.4	580.0	415.2	460.0	520.1
	12.6	85.0	70.1	225.1	225.1	289.0	317.9	529.1	653.4	687.7	750.2
	35.2	129.8	180.0	274.7	420.1	340.3	507.2	634.8	714.3	777.6	912.6
	29.5	156.9	176.7	225.0	289.0	372.6	379.2	529.2	573.3	560.1	520.0
Group 2	29.4	152.1	122.4	186.3	186.3	274.7	485.1	397.0	NA	NA	NA
	41.1	186.2	176.6	274.6	361.0	379.1	440.0	415.2	NA	NA	NA
	48.6	115.3	90.8	176.5	317.9	421.2	529.2	388.8	629.0	NA	NA
	24.5	143.7	115.0	90.7	194.3	559.6	629.3	573.3	540.0	NA	NA
	66.7	289.0	215.6	268.8	388.8	487.4	551.3	767.1	677.6	846.4	634.9
	14.4	84.7	135.2	191.2	176.4	356.4	397.1	551.4	605.0	480.0	634.8
	10.8	70.0	80.0	118.3	156.8	215.6	268.8	346.8	551.3	946.4	440.0
	11.3	15.0	205.8	289.0	346.8	529.2	629.2	551.3	714.2	772.6	806.4
	18.0	56.7	115.3	96.8	177.5	268.8	320.0	372.6	487.4	573.3	683.6
	60.0	166.6	166.7	324.0	420.0	440.0	634.8	500.0	289.0	560.0	748.8
Group 3	66.6	147.0	260.1	420.0	460.0	653.4	806.4	NA	NA	NA	NA
	40.5	156.8	65.0	84.7	191.2	291.5	400.0	NA	NA	NA	NA
	12.5	108.0	96.8	186.2	202.5	213.8	379.1	379.0	433.2	379.0	500.0
	23.4	129.6	176.5	196.6	320.0	397.1	500.0	687.7	767.1	806.4	937.5
	22.2	65.0	176.4	191.3	213.8	274.6	405.0	520.0	796.6	978.7	864.0
	11.2	52.9	70.0	129.6	152.1	303.5	415.0	440.0	556.7	812.5	1014.0
	11.4	115.2	65.1	32.0	10.8	3.2	1.4	0.0	0.0	0.0	0.0
	22.1	55.0	115.2	55.0	93.6	118.8	118.3	230.4	217.6	243.2	217.6
	32.0	44.6	108.9	258.8	247.5	405.0	372.6	388.0	451.3	580.0	573.3
	10.0	118.3	166.6	176.4	186.2	340.2	361.0	556.6	556.6	268.8	346.8

Group 1 received injections of tissue culture medium around the growing tumor,
Group 2 received injections of tissue culture medium and normal spleen cells,
Group 3 received injections of normal spleen cells, immune RNA and tumor antigen.

comparison, the value of Srivastava's likelihood ratio statistic is 1.34, also with 22 degrees of freedom; and, the nonparametric directional test statistic of Koziol *et al.* (1981) yields a p-value of .16 for this experiment. More pronounced inhibition of tumor growth with the ternary immunotherapy regimen was achieved in subsequent experiments by optimizing dose levels (Fukushima *et al.* (1982*a*, 1982*b*)).

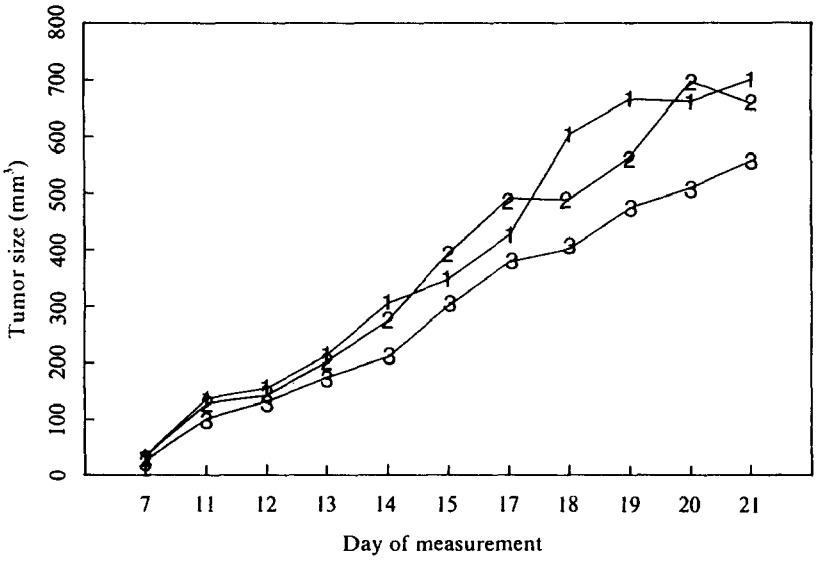

Fig. 1. Mean tumor sizes for three groups.

Acknowledgements

This research was supported in part by grant R01-CA41582 from the National Cancer Institute. This is publication *4577BCR* from the Research Institute of Scripps Clinic, La Jolla, California.

REFERENCES

Cox, D. R. and Hinkley, D. V. (1974). *Theoretical Statistics*, Chapman and Hall, London.

Dwyer, P. S. (1967). Some applications of matrix derivatives in multivariate analysis, *J. Amer. Statist. Assoc.*, **62**, 607–625.

Fukushima, M., Colmerauer, M. E. M., Nayak, S. K., Koziol, J. A. and Pilch, Y. H. (1982*a*). Immunotherapy of a murine colon cancer with syngeneic spleen cells, immune RNA and tumor antigen, *Int. J. Cancer*, **29**, 107–112.

Fukushima, M., Colmerauer, M. E. M., Nayak, S. K., Koziol, J. A. and Pilch, Y. H. (1982*b*). Antitumor effect of syngeneic spleen cells treated with immune RNA and tumor antigen, *Int. J. Cancer*, **29**, 113–117.

Khatri, C. G. (1966). A note on a MANOVA model applied to problems in growth curves, *Ann. Inst. Statist. Math.*, **18**, 75–86.

Kleinbaum, D. G. (1973). A generalization of the growth curve model which allows missing data, *J. Multivariate Anal.*, **3**, 117–124.

Koziol, J. A., Maxwell, D. S., Fukushima, M., Colmerauer, M. E. M. and Pilch, Y. H. (1981). A distribution-free test for tumor-growth curve analyses with application to an animal tumor immunotherapy experiment, *Biometrics*, **37**, 383–390.

Leeper, J. D. and Woolson, R. F. (1982). Testing hypotheses for the growth curve model when the data are incomplete, *J. Statist. Comput. Simulation*, **15**, 97–106.

Potthoff, R. F. and Roy, S. N. (1964). A generalized multivariate analysis of variance model useful especially for growth curve problems, *Biometrika*, **43**, 122–127.

Rao, C. R. (1965). The theory of least squares when the parameters are stochastic and its application to growth curves, *Biometrika*, **52**, 447–458.

Rao, C. R. (1966). Covariance adjustment and related problems in multivariate analysis, *Multivariate Analysis*, (ed. P. R. Krishnaiah), 87–103, Academic Press, New York.

Schwertman, N. C. (1974). The analysis and testing of hypotheses using growth curve data with missing observations, Unpublished PhD. thesis, University of Kentucky.

Srivastava, M. S. (1985). Multivariate data with missing observations, *Comm. Statist. A—Theory Methods*, **14**, 775–792.

Sundberg, R. (1974). Maximum likelihood theory for incomplete data from an exponential family, *Scand. J. Statist.*, **1**, 49–58.