

AN ANALYSIS OF REPEATED MEASUREMENTS ON  
EXPERIMENTAL UNITS IN A TWO-WAY CLASSIFICATION

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## INTRODUCTION

There is a broad class of experiments which can be classified under the general heading of "repeated measurements experiments." The common denominator in these schemes is that a random set of experimental plots has multiple or "repeated" measurements made on them. These experimental plots henceforth will be referred to as subjects, since this type of experiment is commonly found in biological research. Furthermore, the repeated measurements are frequently taken equally spaced in time; thus the repeated aspect or factor of the design will be referred to hereafter as time. The repeated observations in time on the same subject are correlated; hence, the assumption of independent observations cannot be made.

The simplest experiment in this classification consists of a random group of subjects measured on some attribute at several fixed points in time. The associated model for this experiment is a non-hierarchical, two-factor mixed model, one random and one fixed effect. With equal variances in time and with the observations for a given subject equally correlated in time (this will be referred to as symmetry), plus the assumption of normality of the observations, the appropriate test for the time effect may be obtained from the usual analysis of variance for a

non-hierarchical, two-factor, mixed model with uncorrelated errors, Danford and Hughes (1). The random subject effect in the model accounts for the symmetry feature. (1)

When subjects are randomly allocated to various treatments and repeated measurements are made on each subject, the design is partially hierarchical. Under the symmetry assumption, and for equal numbers of subjects in the groups, Harter and Lum (3) have given the appropriate analysis of variance. The random within or nested effect in their model again implies the symmetry feature in the same manner as above. This corresponds to the effects among subjects within treatments in the model considered in this thesis. For the more general case involving unequal numbers of subjects in the groups and under the symmetry assumption, Hughes and Danford (4) have noted the appropriate analysis. It has been shown by Danford, Hughes, and McNee (2) that when the symmetry assumption is not made, some multivariate procedure should be used for testing the effects of time and treatment  $\times$  time. However, the univariate test for treatment effects is still valid.

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(1) The random subject effect gives rise to a constant covariance between different observations in time on the same subject. The ratio of this covariance to the variance of an observation (which is the same for all observations) is the correlation. This is constant over time, which implies the symmetry condition.

Sometimes "treatment" consists of a factorial arrangement of two types of treatments, A and B, say. Again for the case where there is an equal number of subjects for each treatment combination and under the symmetry assumption, the analysis of variance has been given by Harter and Lum (3). The extension to proportionate sub-class numbers can be made as usual, changing from unweighted constraints to weighted constraints. The weights are proportional to the sub-class numbers, and the sums of squares in the analysis are then weighted by these same factors.

The expectation model for this experimental design can be written as:

$$(1) \quad Y_{ijklm} = \mu + \alpha_i + \beta_j + \alpha\beta_{ij} + \gamma_k + \alpha\gamma_{ik} + \beta\gamma_{jk} + \alpha\beta\gamma_{ijk} + s_m(ij) + s\gamma_{mk}(ij)$$

In the equation above, Greek letters represent fixed effects and Latin letters random effects, with:

$\mu$  = the overall mean

$\alpha_i$  = the effect of the  $i^{\text{th}}$  level of treatment A ( $i=1, \dots, r$ )

$\beta_j$  = the effect of the  $j^{\text{th}}$  level of treatment B ( $j=1, \dots, q$ )

$\gamma_k$  = the effect of the  $k^{\text{th}}$  time ( $k=1, \dots, p$ )

$s_m(ij)$  = the effect of the  $m^{\text{th}}$  subject in the  $i, j^{\text{th}}$  group  
( $m=1, \dots, n_{ij}$ ).

Combinations of letters are used to denote the interactions.

The assumptions are:

$$E(s_{m(ij)}) = 0 \text{ for all } i, j, m$$

$$E(s_{m(ij)}, s_{m'(i'j')}) = \begin{cases} \sigma_s^2; & i=i', j=j', m=m' \\ 0; & \text{otherwise} \end{cases}$$

$$E(s_{Y_{mk}(ij)}) = 0 \text{ for all } i, j, k, m$$

$$E(s_{Y_{mk}(ij)}, s_{Y_{m'k'}(i'j')}) = \begin{cases} \sigma_g^2; & i=i', j=j', k=k', m=m' \\ 0; & \text{otherwise} \end{cases}$$

Also, it is assumed that

$$E(s_{Y_{mk}(ij)}, s_{m'(i'j')}) = 0 \text{ for all } i, j, k, m$$

This implies that the variation in response for a subject does not depend on the subject's average response relative to other subjects when no treatment is involved. If this assumption does not seem reasonable, possibly some transformation of the data will make it a reasonable assumption. The analysis of variance is of the form shown in Table 1.

The case of disproportionality of subjects in the factorial arrangement of treatments, which can occur for many reasons, even when the experiment is initially set up with proportionate allocation, poses more difficult analytical problems. The solution of this problem, under the symmetry assumption, is the subject of this thesis.

Table 1. Analysis of variance of a four-way, partially hierarchical, random nested effect design with proportionate cell frequencies

| Source  | df                         | M.Sq    | F             |
|---------|----------------------------|---------|---------------|
| A       | r-1                        | MSA     | MSA/MSS       |
| B       | q-1                        | MSB     | MSB/MSS       |
| AxB     | (r-1)(q-1)                 | MSAxB   | MSAxB/MSS     |
| Subj/AB | n <sub>..</sub> -rq        | MSS     |               |
| Time    | p-1                        | MST     | MST/MSSxT     |
| AxT     | (r-1)(p-1)                 | MSAxT   | MSAxT/MSSxT   |
| BxT     | (q-1)(p-1)                 | MSBxT   | MSBxT/MSSxT   |
| AxBxT   | (r-1)(q-1)(p-1)            | MSAxBxT | MSAxBxT/MSSxT |
| SxT/AB  | (n <sub>..</sub> -rq)(p-1) | MSSxT   |               |

where  $n_{..} = \sum_i \sum_j n_{ij}$

For this situation, the tests of significance of the main effects and interactions depend on the assumptions made about the interactions. It will be shown that by using the general regression approach, tests can be obtained for the three-factor interaction, for all two-factor interactions assuming the three-factor interaction zero, and for all main effects assuming all interactions zero. These are the tests most frequently of interest, since over-all tests of main effects when there are interactions, and tests of the two-factor interactions when there is a three-factor interaction, are usually not of interest. Also, a simplified computing procedure will be developed for the tests mentioned above.

## II

## THE EXPERIMENTAL DESIGN AND EXPECTATION MODEL

The experimental design for the problem to be studied is illustrated by Figure 1. In this design, there are  $r$  levels of treatment A,  $q$  levels of treatment B, and  $p$  observations through time on each of  $n_{ij}$  subjects at the  $i^{\text{th}}$  level of treatment A and the  $j^{\text{th}}$  level of treatment B.

The expectation model for the experimental design considered above is the same as that given in (1). The restrictions imposed on the parameters are:

$$\sum_i v_i \alpha_i = 0$$

$$\sum_j \omega_j \beta_j = 0$$

$$\sum_k \gamma_k = 0$$

$$(2) \quad \sum_i v_i (\alpha\beta)_{ij} = \sum_j \omega_j (\alpha\beta)_{ij} = 0$$

$$\sum_i v_i (\alpha\gamma)_{ik} = \sum_k (\alpha\gamma)_{ik} = 0$$

$$\sum_j \omega_j (\beta\gamma)_{jk} = \sum_k (\beta\gamma)_{jk} = 0$$

$$\sum_i v_i (\alpha\beta\gamma)_{ijk} = \sum_j \omega_j (\alpha\beta\gamma)_{ijk} = \sum_k (\alpha\beta\gamma)_{ijk} = 0$$

Figure 1. Scheme for experimental design of the problem considered

|          |   |     |  |     |                       |   |   |   |   |   |   |          |  |  |  |
|----------|---|-----|--|-----|-----------------------|---|---|---|---|---|---|----------|--|--|--|
|          | $B_1$   | ... | $B_j$  | ... | $B_q$                 |   |   |   |   |   |   |          |  |  |  |
| $A_1$    |   |     |  |     |                       |   |   |   |   |   |   |          |  |  |  |
| •        |   |     |  |     |                       |   |   |   |   |   |   |          |  |  |  |
| •        |   |     |  |     |                       |   |   |   |   |   |   |          |  |  |  |
| •        |   |     |  |     |                       |   |   |   |   |   |   |          |  |  |  |
| $A_i$    |   |     | <table border="1" style="border-collapse: collapse; width: 100%;"> <tr> <td style="border: none;"></td> <td style="border: none;"><math>t_1</math> . . . . . <math>t_p</math></td> </tr> <tr> <td style="border: none;">1</td> <td rowspan="5" style="border: none; text-align: center;"> <p>p observations on each of <math>n_{ij}</math><br/>subjects</p> </td> </tr> <tr> <td style="border: none;">2</td> </tr> <tr> <td style="border: none;">•</td> </tr> <tr> <td style="border: none;">•</td> </tr> <tr> <td style="border: none;">•</td> </tr> <tr> <td style="border: none;"><math>n_{ij}</math></td> <td style="border: none;"></td> </tr> </table> |     | $t_1$ . . . . . $t_p$ | 1 | <p>p observations on each of <math>n_{ij}</math><br/>subjects</p> | 2 | • | • | • | $n_{ij}$ |  |  |  |
|          | $t_1$ . . . . . $t_p$   |     |  |     |                       |   |   |   |   |   |   |          |  |  |  |
| 1        | <p>p observations on each of <math>n_{ij}</math><br/>subjects</p> |     |  |     |                       |   |   |   |   |   |   |          |  |  |  |
| 2        |   |     |  |     |                       |   |   |   |   |   |   |          |  |  |  |
| •        |   |     |  |     |                       |   |   |   |   |   |   |          |  |  |  |
| •        |   |     |  |     |                       |   |   |   |   |   |   |          |  |  |  |
| •        |   |     |  |     |                       |   |   |   |   |   |   |          |  |  |  |
| $n_{ij}$ |   |     |  |     |                       |   |   |   |   |   |   |          |  |  |  |
| •        |   |     |  |     |                       |   |   |   |   |   |   |          |  |  |  |
| •        |   |     |  |     |                       |   |   |   |   |   |   |          |  |  |  |
| •        |   |     |  |     |                       |   |   |   |   |   |   |          |  |  |  |
| $A_r$    |   | ... |  | ... |                       |   |   |   |   |   |   |          |  |  |  |

where the  $v_i$  and  $w_j$  are weighting constants. The values of these constants do not affect any of the tests of significance under the assumption of zero interactions of all orders higher than the order of the interaction or main effect being tested. Scheffe (5) has shown that for the two-way layout the interaction sum of squares and the sums of squares for the main effects assuming zero interactions do not depend on the weights used in the restrictions. The sums of squares in the above tests are shown to be combinations of these sums of squares from the two-way layout. Therefore, they do not depend on the weights. Finally, for testing purposes, it is assumed that the errors  $s_{m(ij)}$  and  $sy_{mk(ij)}$  are normally distributed.

The covariances of the  $Y_{ijklm}$  under the symmetry assumption are:

$$(3) \quad \text{Cov}(Y_{ijklm}, Y_{i'j'k'm'}) = \begin{cases} \sigma^2, & i=i', j=j', k=k', m=m' \\ \rho\sigma^2, & i=i', j=j', k \neq k', m=m' \\ 0, & \text{otherwise} \end{cases}$$

From the expectation model we find:

$$(4) \quad \text{Cov}(Y_{ijklm}, Y_{i'j'k'm'}) = \begin{cases} \sigma_s^2 + \sigma_g^2, & i=i', j=j', k=k', m=m' \\ \sigma_s^2, & i=i', j=j', k \neq k', m=m' \\ 0, & \text{otherwise} \end{cases}$$

Comparing these two,

$$(5) \quad \sigma^2 = \sigma_s^2 + \sigma_g^2$$

$$\rho\sigma^2 = \sigma_s^2$$

For use later, the estimate of  $\sigma_g^2 = (1-\rho)\sigma^2$  will be referred to as Error (b) and the estimate of  $\sigma_g^2 + p\sigma_s^2 = (1+(p-1)\rho)\sigma^2$  as Error (a).

## III

A PROCEDURE BASED ON COMBINING ANALYSES  
FROM EACH TIME

The data at a given time consist of a set of independent observations in a two-way classification with disproportionate sub-class numbers. The expectation model (1), for the set of observations at time  $k$ , can be re-written as

$$(6) \quad Y_{ijkm} = \mu_k + \alpha_{ik} + \beta_{jk} + \alpha\beta_{ijk} + e_{mk}(ij)$$

where the level of  $k$  is constant. The parameters in (6) are defined in terms of the parameters in (1) by

$$\mu_k = \mu + \gamma_k$$

$$\alpha_{ik} = \alpha_i + \alpha\gamma_{ik}$$

$$\beta_{jk} = \beta_j + \beta\gamma_{jk}$$

$$\alpha\beta_{ijk} = \alpha\beta_{ij} + \alpha\beta\gamma_{ijk}$$

$$e_{mk}(ij) = s_m(ij) + s\gamma_{mk}(ij)$$

with the properties and imposed restrictions

$$(7) \quad \sum_i v_i \alpha_{ik} = 0$$

$$\sum_j \omega_j \beta_{jk} = 0$$

$$\sum_i v_i^{(\alpha\beta)}_{ijk} = \sum_j w_j^{(\alpha\beta)}_{ijk} = 0$$

$$E(e_{mk}(ij)) = 0$$

$$E(e_{mk}(ij), e_{m'k}(i'j')) = \begin{cases} \sigma^2, & i=i', j=j', m=m' \\ 0, & \text{otherwise} \end{cases}$$

From equation (5),  $\sigma^2 = \sigma_s^2 + \sigma_g^2$  in (7).

By the method of fitting constants, an analysis of variance of the form given in Table 2 can be calculated separately for each time.

Table 2. Structure of analysis of variance for a two-way disproportionate layout

| Source                           | df         |
|----------------------------------|------------|
| A, corrected for B, ignoring AxB | r-1        |
| B, corrected for A, ignoring AxB | q-1        |
| AxB, corrected for A and B       | (r-1)(q-1) |
| Error                            | n..-rq     |

Also, one can sum over time and perform a similar analysis on the subject means.

In the proposed procedure, the sums of squares of the effects that are averaged over time are obtained by multiplying

the sums of squares from the analysis on the subject means by  $p$ , the number of time measurements, in order to express sums of squares on the basis of an individual observation. Also, in the proposed procedure the sums of squares that include time as a factor (except for the time sum of squares) are obtained by summing over time each of the sums of squares in the analyses of data at a given time and then subtracting the corresponding sum of squares obtained in the "averaged over time" analysis. The sources for these sums of squares are the interactions with time of the respective sources averaged over time. For example, let  $SSA_k$  be the sum of squares for treatment A at time  $k$  and let  $SSA_a$  be the sum of squares for treatment A from the analysis on the subject means. Then, the sum of squares for treatment A would be  $p(SSA_a)$  and the sum of squares for the treatment A by time interaction would be

$$\sum_{k=1}^p SSA_k - p(SSA_a) .$$

Finally, the sum of squares for time can be obtained in the usual manner from the means at each time, averaged over all subjects.

## IV

GENERAL SCHEME OF THE PROPOSED  
PROCEDURE AND AN EXAMPLE

The general scheme of the proposed procedure will be paralleled with an example for clarification. The basic data for the example are given in Table 3.

A. Calculation of the regression sum of squares at a given time

A set of restrictions from (7) must be included in the equations obtained from the expectation model (6) to obtain linear independence. To simplify computations, use a set obtained by letting any one of the  $v_i$  and any one of the  $\omega_j$  equal unity and the others zero. One may set  $v_r$  and  $\omega_q$  equal to unity, the others zero, without loss of generality. This can be written as:

$$(8) \quad v_i = \begin{cases} 0, & i \neq r \\ 1, & i = r \end{cases}, \quad \omega_j = \begin{cases} 0, & j \neq q \\ 1, & j = q \end{cases}$$

For the example, this is equivalent to setting

$$\alpha_{3k} = \beta_{2k} = \alpha\beta_{12k} = \alpha\beta_{22k} = \alpha\beta_{31k} = \alpha\beta_{32k} = 0.$$

Then, the equations can be written in matrix form as:

$$(9) \quad Y_k = P_k \Lambda_k + E_k$$

Table 3. Basic data for the example

|                | B <sub>1</sub> |                |                | B <sub>2</sub> |                |                |
|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                | t <sub>1</sub> | t <sub>2</sub> | t <sub>3</sub> | t <sub>1</sub> | t <sub>2</sub> | t <sub>3</sub> |
| A <sub>1</sub> | 39             | 36             | 38             | 36             | 39             | 38             |
|                | 38             | 42             | 30             | 31             | 34             | 28             |
|                | 40             | 28             | 33             | 46             | 44             | 35             |
|                |                |                |                | 44             | 41             | 36             |
|                |                |                |                | 32             | 34             | 34             |
| A <sub>2</sub> | 56             | 51             | 53             | 39             | 34             | 32             |
|                | 54             | 40             | 45             | 54             | 56             | 50             |
|                | 50             | 45             | 49             |                |                |                |
|                | 32             | 33             | 31             |                |                |                |
| A <sub>3</sub> | 38             | 41             | 37             | 55             | 48             | 46             |
|                | 39             | 33             | 40             | 39             | 44             | 30             |
|                | 51             | 38             | 39             | 49             | 36             | 42             |
|                |                |                |                | 44             | 39             | 22             |

The vectors  $Y_k$ ,  $\Lambda_k$ , and  $E_k$  are the vector of  $n_{..}$  observations at time  $k$ , the vector of  $rq$  non-zero parameters at time  $k$  that are to be estimated, and the vector of  $n_{..}$  errors at time  $k$ , respectively. The  $rq$  non-zero parameters in  $\Lambda_k$  are defined by the restrictions in (8). This vector is given in (10). The  $n_{..} \times rq$  matrix  $P_k$  is a matrix of  $n_{..}$  row vectors  $H_{ij}^T$ , which are the transposes of the vectors,  $H_{ij}$ . The vector  $H_{ij}$  is a vector of  $rq$  elements with each element either 0 or 1 such that the expected value of  $Y_{ijkm}$  is  $H_{ij}^T \Lambda_k$ . The matrix  $P_k$  and the vector  $H_{ij}$  are also shown in (10).

$$(10) \quad P_k = \left[ \begin{array}{c} H_{11}^T \\ \cdot \\ \cdot \\ H_{11}^T \\ \cdot \\ H_{12}^T \\ \cdot \\ \cdot \\ H_{12}^T \\ \cdot \\ \cdot \\ H_{rq}^T \\ \cdot \\ \cdot \\ H_{rq}^T \end{array} \right] \left\{ \begin{array}{l} n_{11} \\ n_{12} \\ n_{rq} \end{array} \right. ; \quad H_{ij} = \left[ \begin{array}{c} h_{ij1} \\ h_{ij2} \\ \cdot \\ \cdot \\ h_{ijs} \end{array} \right] , \quad \Lambda_k = \left[ \begin{array}{c} \mu_k \\ \alpha_{1k} \\ \cdot \\ \cdot \\ \alpha_{r'k} \\ \beta_{1k} \\ \cdot \\ \cdot \\ \beta_{q'k} \\ \alpha\beta_{11k} \\ \cdot \\ \cdot \\ \alpha\beta_{r'q'k} \end{array} \right]$$

where  $s=rq$ ,  $r'=r-1$ , and  $q'=q-1$ . The matrix  $P_k$  is the same for any time,  $k$ , and is subscripted only to distinguish it

from the matrix for the full set of observations as defined later. The  $P_k$  and the form of  $Y_k$  and  $\Lambda_k$  for the example are given in Table 4.

From the normal equations, the regression sum of squares is

$$\begin{aligned}
 (11) \quad SSR_k &= (P_k^T Y_k)^T (P_k^T P_k)^{-1} (P_k^T Y_k) \\
 &= \left( \sum_{ij} Y_{ijk} \cdot H_{ij} \right)^T \left( \sum_{ij} n_{ij} H_{ij} H_{ij}^T \right)^{-1} \left( \sum_{ij} Y_{ijk} \cdot H_{ij} \right) \\
 &= G_k^T C^{-1} G_k
 \end{aligned}$$

where

$$\begin{aligned}
 (12) \quad G_k &= \sum_{ij} Y_{ijk} \cdot H_{ij} \\
 C &= \sum_{ij} n_{ij} H_{ij} H_{ij}^T
 \end{aligned}$$

and the dot indicates summation over the index it replaces.  $G_k$  is a vector of  $rq$  elements and  $C$  is an  $rq \times rq$  matrix of full rank. Table 5 gives the  $G_k$  vectors and the  $C$  matrix for the example.

#### B. Method of calculating the regression sum of squares assuming some of the parameters to be zero

To obtain the regression sum of squares at time  $k$  under the assumption that some of the parameters (e.g., the  $\alpha\beta_{ijk}$ ) are zero, the expectation model (6) is reduced by eliminating

Table 4.  $P_k$ ,  $Y_k$ , and  $\Lambda_k$  for the example

|             |             |   |         |            |   |               |                     |
|-------------|-------------|---|---------|------------|---|---------------|---------------------|
| $P_k =$     | 1 1 0 1 1 0 | ; | $Y_k =$ | $Y_{11k1}$ | ; | $\Lambda_k =$ | $\mu_k$             |
|             | 1 1 0 1 1 0 |   |         | $Y_{11k2}$ |   |               | $\alpha_{1k}$       |
|             | 1 1 0 1 1 0 |   |         | $Y_{11k3}$ |   |               | $\alpha_{2k}$       |
|             | 1 1 0 0 0 0 |   |         | $Y_{12k1}$ |   |               | $\beta_{1k}$        |
|             | 1 1 0 0 0 0 |   |         | $Y_{12k2}$ |   |               | $\alpha\beta_{11k}$ |
|             | 1 1 0 0 0 0 |   |         | $Y_{12k3}$ |   |               | $\alpha\beta_{21k}$ |
|             | 1 1 0 0 0 0 |   |         | $Y_{12k4}$ |   |               |                     |
|             | 1 1 0 0 0 0 |   |         | $Y_{12k5}$ |   |               |                     |
|             | 1 0 1 1 0 1 |   |         | $Y_{21k1}$ |   |               |                     |
|             | 1 0 1 1 0 1 |   |         | $Y_{21k2}$ |   |               |                     |
|             | 1 0 1 1 0 1 |   |         | $Y_{21k3}$ |   |               |                     |
|             | 1 0 1 1 0 1 |   |         | $Y_{21k4}$ |   |               |                     |
|             | 1 0 1 0 0 0 |   |         | $Y_{22k1}$ |   |               |                     |
|             | 1 0 1 0 0 0 |   |         | $Y_{22k2}$ |   |               |                     |
|             | 1 0 0 1 0 0 |   |         | $Y_{31k1}$ |   |               |                     |
|             | 1 0 0 1 0 0 |   |         | $Y_{31k2}$ |   |               |                     |
|             | 1 0 0 1 0 0 |   |         | $Y_{31k3}$ |   |               |                     |
|             | 1 0 0 0 0 0 |   |         | $Y_{32k1}$ |   |               |                     |
|             | 1 0 0 0 0 0 |   |         | $Y_{32k2}$ |   |               |                     |
|             | 1 0 0 0 0 0 |   |         | $Y_{32k3}$ |   |               |                     |
| 1 0 0 0 0 0 | $Y_{32k4}$  |   |         |            |   |               |                     |

Table 5. The  $G_k$  vectors and the C matrix for the example

$$G_1 = \begin{bmatrix} 906 \\ 306 \\ 285 \\ 437 \\ 117 \\ 192 \end{bmatrix} ; \quad G_2 = \begin{bmatrix} 836 \\ 298 \\ 259 \\ 387 \\ 106 \\ 169 \end{bmatrix} ; \quad G_3 = \begin{bmatrix} 787 \\ 271 \\ 260 \\ 395 \\ 101 \\ 178 \end{bmatrix}$$

$$C = \begin{bmatrix} 21 & 8 & 6 & 10 & 3 & 4 \\ 8 & 8 & 0 & 3 & 3 & 0 \\ 6 & 0 & 6 & 4 & 0 & 4 \\ 10 & 3 & 4 & 10 & 3 & 4 \\ 3 & 3 & 0 & 3 & 3 & 0 \\ 4 & 0 & 4 & 4 & 0 & 4 \end{bmatrix}$$

the parameters assumed zero. This eliminates the associated elements in the  $\Lambda_k$  and  $H_{ij}$  vectors in equation (9). Thus, to calculate the regression sum of squares for the mean and the treatment A and treatment B effects, one merely eliminates the last  $(r-1)(q-1)$  elements in  $\Lambda_k$  and in the  $H_{ij}$ . These are the elements associated with the parameters  $\{\alpha\beta_{ijk}\}$ . This has the effect of eliminating the corresponding elements of the  $G_k$  vector and the corresponding rows and columns of the C matrix in equation (11).

Let  $G_{0k}$  and  $C_0$  be the vector  $G_k$  and matrix C in (11) when none of the parameters in (6) is assumed zero. Call this the full model. Let  $G_{1k}$  and  $C_1$  be the vector  $G_k$  and the matrix C when the  $\alpha\beta_{ijk}$  are assumed zero. Similarly define  $G_{2k}$  and  $C_2$  when the  $\alpha\beta_{ijk}$  and the  $\beta_{jk}$  are assumed zero,  $G_{3k}$  and  $C_3$  when the  $\alpha\beta_{ijk}$  and the  $\alpha_{ik}$  are assumed zero, and  $G_{4k}$  and  $C_4$  when the  $\alpha\beta_{ijk}$ , the  $\alpha_{ik}$ , and the  $\beta_{jk}$  are assumed zero. Then, the regression sums of squares needed for an analysis of data at time k can be written as

$$(13) \quad SS(M_k, A_k, B_k, Ax B_k) = G_{0k}^T C_0^{-1} G_{0k}$$

$$SS(M_k, A_k, B_k) = G_{1k}^T C_1^{-1} G_{1k}$$

$$SS(M_k, A_k) = G_{2k}^T C_2^{-1} G_{2k}$$

$$SS(M_k, B_k) = G_{3k}^T C_3^{-1} G_{3k}$$

$$SS(M_k) = G_{4k}^T C_4^{-1} G_{4k}$$

The symbols in the parentheses indicate constants fitted;  $M_k$  stands for  $\mu_k$ ,  $A_k$  for the  $\{\alpha_{ik}\}$ ,  $B_k$  for the  $\{\beta_{jk}\}$ , and  $AxB_k$  for the  $\{\alpha\beta_{ijk}\}$ . Four of these sums of squares may be calculated more easily as

$$(14) \quad SS(M_k, A_k, B_k, AxB_k) = \sum_{ij} \sum_{jk} Y_{ijk}^2 / n_{ij}$$

$$SS(M_k, A_k) = \sum_i Y_{i.k}^2 / n_{i.}$$

$$SS(M_k, B_k) = \sum_j Y_{.jk}^2 / n_{.j}$$

$$SS(M_k) = Y_{..k}^2 / n_{..}$$

To calculate  $SS(M_k, A_k, B_k)$ , perform the multiplication

$G_{1k}^T C_1^{-1} G_{1k}$ , with  $C_1$  and  $G_{1k}$  defined as

$$(15) \quad C_1 = \begin{bmatrix} n_{..} & n_{.1} & n_{.2} & \dots & n_{.r} & n_{.1} & n_{.2} & \dots & n_{.q} \\ n_{.1} & n_{11} & 0 & \dots & 0 & n_{11} & n_{12} & \dots & n_{1q} \\ n_{.2} & 0 & n_{22} & \dots & \dots & n_{21} & n_{22} & \dots & n_{2q} \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ n_{.r} & 0 & \dots & 0 & n_{r.} & n_{r1} & n_{r2} & \dots & n_{rq} \\ n_{.1} & n_{11} & n_{21} & \dots & n_{r1} & n_{.1} & 0 & \dots & 0 \\ n_{.2} & n_{12} & n_{22} & \dots & n_{r2} & 0 & n_{.2} & \dots & \dots \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ n_{.q} & n_{1q} & n_{2q} & \dots & n_{rq} & 0 & \dots & 0 & n_{.q} \end{bmatrix}; \quad G_{1k} = \begin{bmatrix} Y_{..k} \\ Y_{.1k} \\ Y_{.2k} \\ \vdots \\ Y_{.rk} \\ Y_{.1k} \\ Y_{.2k} \\ \vdots \\ Y_{.qk} \end{bmatrix}$$

where  $r' = r-1$  and  $q' = q-1$ .

Using equations (13) through (15) and similar equations for the average-over-time effects, the sums of squares by the proposed procedure are shown in Table 6. Following the usual notation herein,  $C_{1.} = \sum_k G_{1k}$ .

For the example,  $C_1$  is obtained from Table 5:

$$C_1 = \begin{bmatrix} 21 & 8 & 6 & 10 \\ 8 & 8 & 0 & 3 \\ 6 & 0 & 6 & 4 \\ 10 & 3 & 4 & 10 \end{bmatrix}$$

Its inverse is:

$$C_1^{-1} = \begin{bmatrix} .180169286 & -.147521161 & -.122128174 & -.087061669 \\ -.147521161 & .268440145 & .140266022 & .010882709 \\ -.122128174 & .140266022 & .321039903 & -.048367593 \\ -.087061669 & .010882709 & -.048367593 & .203143894 \end{bmatrix}$$

The  $G_{1k}$ , from Table 5, are:

$$G_{11} = \begin{bmatrix} 906 \\ 306 \\ 285 \\ 437 \end{bmatrix} ; \quad G_{12} = \begin{bmatrix} 836 \\ 298 \\ 259 \\ 387 \end{bmatrix} ; \quad G_{13} = \begin{bmatrix} 787 \\ 271 \\ 260 \\ 395 \end{bmatrix}$$

From these quantities, we calculate:

Table 6. Sums of squares by the proposed procedure

| Source   | df              | Sum of Squares   |
|----------|-----------------|--|
| A        | r-1             | $G_1^T \cdot C_1^{-1} G_1 \cdot / p - \sum_j Y_{\cdot j \cdot \cdot}^2 / p n_{\cdot j} = (1)$            |
| B        | q-1             | $G_1^T \cdot C_1^{-1} G_1 \cdot / p - \sum_i Y_{i \cdot \cdot \cdot}^2 / p n_{i \cdot} = (2)$            |
| AxB      | (r-1)(q-1)      | $\sum_{ij} Y_{ij \cdot \cdot}^2 / p n_{ij} - G_1^T \cdot C_1^{-1} G_1 \cdot = (3)$                       |
| Error(a) | n..-rq          | $\sum_{ijm} Y_{ij \cdot m}^2 / p - \sum_{ij} Y_{ij \cdot \cdot}^2 / p n_{ij} = (4)$                      |
| Time     | p-1             | $\sum_k Y_{\cdot \cdot k \cdot}^2 / n_{\cdot \cdot} - Y_{\cdot \cdot \cdot \cdot}^2 / p n_{\cdot \cdot}$ |
| AxT      | (r-1)(p-1)      | $\sum_k [G_{1k}^T C_1^{-1} G_{1k} - \sum_j Y_{\cdot j k \cdot}^2 / n_{\cdot j}] = (1)$                   |
| BxT      | (q-1)(p-1)      | $\sum_k [G_{1k}^T C_1^{-1} G_{1k} - \sum_i Y_{i \cdot k \cdot}^2 / n_{i \cdot}] = (2)$                   |
| AxBxT    | (r-1)(q-1)(p-1) | $\sum_k [\sum_{ij} Y_{ijk \cdot}^2 / n_{ij} - G_{1k}^T C_1^{-1} G_{1k}] = (3)$                           |
| Error(b) | (n..-rq)(p-1)   | $\sum_{ijkm} Y_{ijkm}^2 - \sum_{ijk} Y_{ijk \cdot}^2 / n_{ij} = (4)$                                     |

$$G_{11}^T C_1^{-1} G_{11} = 39,418.54$$

$$G_{12}^T C_1^{-1} G_{12} = 33,459.44$$

$$G_{13}^T C_1^{-1} G_{13} = 29,830.74$$

$$G_1^T C_1^{-1} G_1 / p = 102,223.80$$

$$\sum_k G_{1k}^T C_1^{-1} G_{1k} = 102,708.72$$

Furthermore:

$$\sum_i y_{i\dots}^2 / p n_{i\dots} = 102,217.80$$

$$\sum_j y_{\dots j}^2 / p n_{\dots j} = 101,535.06$$

$$\sum_{ij} y_{ij\dots}^2 / p n_{ij\dots} = 102,236.43$$

$$\sum_k y_{\dots k}^2 / n_{\dots} = 101,861.95$$

$$\sum_{ik} y_{i\dots k}^2 / n_{i\dots} = 102,626.89$$

$$\sum_{jk} y_{\dots jk}^2 / n_{\dots j} = 101,969.57$$

$$\sum_{ijk} y_{ijk\dots}^2 / n_{ijk\dots} = 102,761.92$$

$$\sum_{ijm} y_{ij\dots m}^2 / p = 104,187.00$$

$$\sum_{ijmk} y_{ijkm}^2 = 105,277.00$$

$$Y_{\dots}^2 / pn_{\dots} = 101,521.29$$

The completed analysis of variance for the example is given in Table 7.

Table 7. Analysis of variance for the example

| Source    | df | S.Sq.    | M.Sq.  | F    | P     |
|-----------|----|----------|--------|------|-------|
| A         | 2  | 688.74   | 344.37 | 2.65 | >.05  |
| B         | 1  | 6.00     | 6.00   | .05  | >.05  |
| AxB       | 2  | 12.63    | 6.31   | .05  | >.05  |
| Error (a) | 15 | 1,950.57 | 130.04 |      |       |
| Time      | 2  | 340.66   | 170.33 | 9.05 | <.001 |
| AxT       | 4  | 50.41    | 12.60  | .67  | >.05  |
| BxT       | 2  | 75.83    | 37.92  | 2.01 | >.05  |
| AxBxT     | 4  | 40.57    | 10.14  | .54  | >.05  |
| Error (b) | 30 | 564.51   | 18.82  |      |       |

VERIFICATION OF THE COMPUTING FORMS FOR THE SUMS OF  
SQUARES AVERAGED OVER TIME

For the sums of squares "averaged over time" in Table 6, consider the set of means  $\{\bar{Y}_{ij \cdot m}\}$ , which is the average of the  $Y_{ijkm}$  over time. The expectation model, derived from equation (1) using the restrictions in (2), is

$$(16) \quad \bar{Y}_{ij \cdot m} = \mu + \alpha_i + \beta_j + \alpha\beta_{ij} + s_m(ij) + \bar{s}_{Y_{m \cdot}}(ij)$$

The  $s_m(ij)$  and  $\bar{s}_{Y_{m \cdot}}(ij)$  are inseparable and can be considered as a single error term,

$$(17) \quad e_m(ij) = s_m(ij) + \bar{s}_{Y_{m \cdot}}(ij) \cdot$$

From the assumptions under (1),

$$(18) \quad E(e_m(ij)) = 0$$

$$E(e_m(ij), e_{m'}(i'j')) = \begin{cases} \sigma_s^2 + \sigma_g^2/p; & i=i', j=j', m=m' \\ 0; & \text{otherwise} \end{cases}$$

Also, the  $\{e_m(ij)\}$  are normally distributed which follows from the normality assumptions on the  $\{s_m(ij)\}$  and  $\{s_{Y_{mk}}(ij)\}$ .

Let  $Z_{ijm} = \bar{Y}_{ij \cdot m}$ . Then the expectation model (16) can be written as

$$(19) \quad Z_{ijm} = \mu + \alpha_i + \beta_j + \alpha\beta_{ij} + e_m(ij) \cdot$$

This is the fixed effects expectation model for a two-way classification with disproportionate sub-class numbers. The regression sum of squares for all effect parameters is

$$(20) \quad SS(M,A,B,AXB) = \sum_{ij} z_{ij\cdot}^2 / n_{ij} \quad .$$

Also, the regression sum of squares ignoring the B classification is

$$(21) \quad SS(M,A) = \sum_i z_{i\cdot\cdot}^2 / n_{i\cdot} \quad .$$

Similarly,

$$(22) \quad SS(M,B) = \sum_j z_{\cdot j\cdot}^2 / n_{\cdot j}$$

The sum of squares for error under the full model (for all parameters in (19) ) is

$$(23) \quad SSE = \sum_{ijm} (z_{ijm} - \bar{z}_{ij\cdot})^2$$

To calculate the sum of squares  $SS(M,A,B)$  for  $\mu$  and the  $\{\alpha_i\}$  and  $\{\beta_j\}$ , omit the  $\{\alpha\beta_{ij}\}$  parameters from (19). Then, impose the restrictions given by (8) to obtain a reduced set of normal equations of full rank in  $\mu$  and the  $\{\alpha_i\}$  and  $\{\beta_j\}$ . Using matrix notation and substituting the  $\bar{V}_{ij\cdot m}$  for the  $z_{ijm}$  in the vector of sums, this sum of squares can be written as

$$(24) \quad SS(M,A,B) = \left( \sum_k G_{1k} \right)^T C_1^{-1} \left( \sum_k G_{1k} \right) / p^2 = \bar{G}_1^T \cdot C_1^{-1} \bar{G}_1.$$

where  $G_{1k}$  and  $C_1$  are as defined in equation (15) and

$$\bar{G}_{1\cdot} = \frac{1}{p} \sum_k G_{1k}$$

The sums of squares from the  $Z_{ijm}$  means can be put on a single observation basis by multiplying by  $p$ , the number of observations in the means. The analysis of variance on a per-observation basis, adjusting the sums of squares for the A and B effects for each other, and the interaction for both the A and B effects, can be obtained from equations (20) through (24) and is given in Table 8.

Table 8. "Averaged over time" analysis of variance

| Source | df                    | Sum of Squares  |
|--------|-----------------------|---|
| A      | $r-1$                 | $p [\bar{G}_{1\cdot}^T \cdot C_1^{-1} \bar{G}_{1\cdot} - \sum_j z_{\cdot j}^2 / n_{\cdot j}]$ |
| B      | $q-1$                 | $p [\bar{G}_{1\cdot}^T \cdot C_1^{-1} \bar{G}_{1\cdot} - \sum_i z_{i\cdot}^2 / n_{i\cdot}]$   |
| AxB    | $(r-1)(q-1)$          | $p [\sum_{ij} z_{ij\cdot}^2 / n_{ij} - \bar{G}_{1\cdot}^T \cdot C_1^{-1} \bar{G}_{1\cdot}]$   |
| Error  | $n_{\cdot\cdot} - rq$ | $p [\sum_{ijm} z_{ijm}^2 - \sum_{ij} z_{ij\cdot}^2 / n_{ij}]$                                 |

Substituting  $\bar{Y}_{ij\cdot m}$  for  $Z_{ijm}$ , the sums of squares in Table 8 can be shown to be equivalent to the sums of squares "averaged over time" in Table 6. The error line in Table 8 is the error (a) line in Table 6, and is an estimate of  $\sigma_g^2 + p\sigma_s^2$ .

## VI

VERIFICATION OF THE COMPUTING FORMS FOR THE SUMS OF  
SQUARES IN WHICH TIME IS A FACTOR

The sums of squares with time as a factor involve correlated observations. This correlation derives from the random variable,  $s_{m(ij)}$ . To eliminate the random variable  $s_{m(ij)}$  and to obtain linear independence in time, define

$$(25) \quad X_{ijklm} = Y_{ijklm} - Y_{ijpjm} \quad k=1, \dots, p'; \quad p'=p-1 .$$

These  $X_{ijklm}$  are independent of the  $\bar{Y}_{ij \cdot m}$ , which are used to calculate the sums of squares averaged over time. <sup>(2)</sup>

Therefore, no adjustments for these average effects are required. From (1) and (16), and using the restrictions on the parameters as given in (2), the  $X_{ijklm}$  can be written in parametric form as

$$(26) \quad X_{ijklm} = (\gamma_k - \gamma_p) + (\alpha\gamma_{ik} - \alpha\gamma_{ip}) + (\beta\gamma_{jk} - \beta\gamma_{jp}) + \\ (\alpha\beta\gamma_{ijk} - \alpha\beta\gamma_{ijp}) + (s\gamma_{mk(ij)} - s\gamma_{mp(ij)})$$

with

---

(2) The  $X_{ijklm}$  are uncorrelated with the  $\bar{Y}_{ij \cdot m}$ . Thus, with the normal assumption, they are independent.



of  $S$ , is a symmetric matrix of order  $p'$ . Throughout this thesis, the elements below the main diagonal in symmetric matrices are not shown.

Re-define the parameters as differences in parameters at times  $k$  and  $p$  as shown in equation (26). The observation equations in matrix form are then

$$(31) \quad X = P^* \Lambda^* + E,$$

where  $X$  is the vector of  $p'n..$  elements defined in (29),  $P^*$  as a  $p'n.. \times p'$  ( $rq + r + q + 1$ ) matrix,  $\Lambda^*$  is a vector of  $p'(rq + r + q + 1)$  parameters, and  $E$  is a vector of  $p'n..$  errors,  $SY_{mk}(ij) - SY_{mp}(ij)$ . Using restrictions for the re-defined parameters obtained by using specific values of weights in (8) with the restrictions in (2), linear independence obtains and the equations in (31) may be written as

$$(32) \quad X = PA + E$$

where  $P$  is a  $p'n.. \times p'rq$  matrix and  $A$  is a vector of  $p'rq$  parameters.  $P$  can be written as a vector of  $n..$  sub-matrices,  $D_{ij}$ , where  $D_{ij}$  is a  $p' \times p'$  diagonal matrix of sub-vectors,  $H_{ij}^T$ , and  $H_{ij}$  is the vector of  $rq$  elements with each element either 0 or 1 that was defined above (10). Also,  $A$  can be written as a vector of sub-vectors,  $\Lambda_k - \Lambda_p$  where  $\Lambda_k$  is defined above and in (10).



The covariance matrix of  $\hat{\Lambda}$  is

$$(37) \quad \sum_{\lambda} = (P^T S^{-1} P)^{-1} P^T S^{-1} \sum_X S^{-1} P (P^T S^{-1} P)^{-1} \\ = (P^T S^{-1} P)^{-1} \sigma_g^2 ,$$

and the regression sum of squares is

$$(38) \quad SSR = \hat{\Lambda}^T P^T S^{-1} P \hat{\Lambda} \\ = \hat{\Lambda}^T P^T S^{-1} X .$$

From equations (29), (30), and (33),

$$(39) \quad P^T S^{-1} = [D_{11}^T Q^{-1}, \dots, D_{11}^T Q^{-1}, D_{12}^T Q^{-1}, \dots, D_{12}^T Q^{-1}, \dots, D_{rq}^T Q^{-1}, \\ \dots, D_{rq}^T Q^{-1}]$$

$$P^T S^{-1} P = \sum_{ij} n_{ij} D_{ij}^T Q^{-1} D_{ij}$$

$$P^T S^{-1} X = \sum_{ij} D_{ij}^T Q^{-1} X_{ij} .$$

where  $X_{ij}^T = \sum_m X_{ijm}^T = [X_{ij1}, \dots, X_{ij2}, \dots, X_{ijp}] .$

The matrix  $Q$ , given in equation (30), has the inverse

$$(40) \quad Q^{-1} = \frac{1}{p} \begin{bmatrix} p-1 & -1 & \dots & -1 \\ & \cdot & \cdot & \cdot \\ & & \cdot & \cdot \\ & & & \cdot \\ & & & & -1 \\ & & & & & p-1 \end{bmatrix}$$

Using equation (40) and  $D_{ij}$ , as given in equation (33), one obtains

$$(41) \quad D_{ij}^T Q^{-1} = \frac{1}{p} \begin{bmatrix} (p-1)H_{ij} & -H_{ij} & \dots & -H_{ij} \\ & \cdot & \cdot & \cdot \\ & & \cdot & \cdot \\ & & & \cdot \\ & & & & -H_{ij} \\ & & & & & (p-1)H_{ij} \end{bmatrix}$$

Post-multiplying equation (41) by  $D_{ij}$ , we find

$$(42) \quad D_{ij}^T Q^{-1} D_{ij} = \frac{1}{p} \begin{bmatrix} (p-1)H_{ij}H_{ij}^T & -H_{ij}H_{ij}^T & \dots & -H_{ij}H_{ij}^T \\ & \cdot & \cdot & \cdot \\ & & \cdot & \cdot \\ & & & \cdot \\ & & & & -H_{ij}H_{ij}^T \\ & & & & & (p-1)H_{ij}H_{ij}^T \end{bmatrix}$$

where  $D_{ij}^T Q^{-1} D_{ij}$  is a  $p' \times p'$  matrix of sub-matrices and  $H_{ij}H_{ij}^T$  is an  $r_{ij} \times r_{ij}$  matrix with elements that are 0 or 1 with proportionate rows and proportionate columns. Then, from equations (39) and (42),  $P^T S^{-1} P$  can be written as

$$(43) \quad P^T S^{-1} P = \begin{bmatrix} (p-1) \sum_{ij} n_{ij} H_{ij} H_{ij}^T & - \sum_{ij} n_{ij} H_{ij} H_{ij}^T & \dots & - \sum_{ij} n_{ij} H_{ij} H_{ij}^T \\ & \cdot & \cdot & \cdot \\ & & \cdot & \cdot \\ & & & \cdot \\ & & & & - \sum_{ij} n_{ij} H_{ij} H_{ij}^T \\ & & & & & (p-1) \sum_{ij} n_{ij} H_{ij} H_{ij}^T \end{bmatrix}$$

From equation (12),  $\sum_{ij} n_{ij} H_{ij} H_{ij}^T$  is defined as  $C$ . Therefore, equation (43) can be written as

$$(44) \quad P^T S^{-1} P = \begin{bmatrix} (p-1)C & -C & \dots & \dots & -C \\ & \ddots & \ddots & \ddots & \ddots \\ & & & & \ddots \\ & & & & -C \\ & & & & (p-1)C \end{bmatrix}$$

Post-multiplying equation (41) by  $X_{ij}^*$ , where  $X_{ij}^*$  is defined in equation (29),

$$(45) \quad D_{ij}^T Q^{-1} X_{ij}^* = \frac{1}{p} \begin{bmatrix} (pX_{ij1}^* - X_{ij}^{\dots}) H_{ij} \\ (pX_{ij2}^* - X_{ij}^{\dots}) H_{ij} \\ \vdots \\ (pX_{ijp}^* - X_{ij}^{\dots}) H_{ij} \end{bmatrix}$$

where  $D_{ij}^T Q^{-1} X_{ij}^*$  is a vector of  $p-1$  sub-vectors and each sub-vector has  $rq$  elements.

Summing  $D_{ij}^T Q^{-1} X_{ij}^*$  over  $i$  and  $j$ , one can then write, from equation (39),

$$(46) \quad P^T S^{-1} X = \frac{1}{P} \begin{bmatrix} \sum_{ij} (pX_{ij1} - X_{ij\cdot\cdot}) H_{ij} \\ \sum_{ij} (pX_{ij2} - X_{ij\cdot\cdot}) H_{ij} \\ \vdots \\ \sum_{ij} (pX_{ijp} - X_{ij\cdot\cdot}) H_{ij} \end{bmatrix}$$

From equation (12), substituting  $Y_{ijk} - Y_{ijp}$  for  $X_{ijk}$ ,

$$(47) \quad \sum_{ij} X_{ijk} H_{ij} = G_k - G_p$$

$$\sum_{ij} X_{ij\cdot\cdot} H_{ij} = G_{\cdot\cdot} - pG_p$$

Using equation (47), equation (46) can be written as

$$(48) \quad P^T S^{-1} X = \begin{bmatrix} G_1 - \bar{G} \\ G_2 - \bar{G} \\ \vdots \\ G_p - \bar{G} \end{bmatrix}$$

To obtain a solution of the equation for  $\hat{\Lambda}$ , note that the inverse of  $P^T S^{-1} P$  is

$$(49) \quad (P^T S^{-1} P)^{-1} = \begin{bmatrix} 2c^{-1} & c^{-1} & \dots & c^{-1} \\ & \ddots & \ddots & \vdots \\ & & \ddots & c^{-1} \\ & & & 2c^{-1} \end{bmatrix}$$

Then, from equations (36), (48), and (49),

$$(50) \quad \hat{\lambda} = \begin{bmatrix} 2c^{-1} & c^{-1} & \dots & c^{-1} \\ & \ddots & \ddots & \vdots \\ & & \ddots & c^{-1} \\ & & & 2c^{-1} \end{bmatrix} \begin{bmatrix} g_1 - \bar{g} \\ g_2 - \bar{g} \\ \vdots \\ g_{p'} - \bar{g} \end{bmatrix}$$

$$\hat{\lambda} = \begin{bmatrix} \sum_{i=1}^{p'} c^{-1}(g_i - \bar{g}) + c^{-1}(g_1 - \bar{g}) \\ \dots \\ \sum_{i=1}^{p'} c^{-1}(g_i - \bar{g}) + c^{-1}(g_{p'} - \bar{g}) \end{bmatrix}$$

$$\hat{\lambda} = \begin{bmatrix} c^{-1}(g_1 - g_{p'} - p' \bar{g} + g_1 - \bar{g}) \\ \dots \\ c^{-1}(g_1 - g_{p'} - p' \bar{g} + g_{p'} - \bar{g}) \end{bmatrix}$$

$$\hat{\lambda} = \begin{bmatrix} c^{-1}(g_1 - g_p) \\ c^{-1}(g_2 - g_p) \\ \dots \\ c^{-1}(g_{p'} - g_p) \end{bmatrix}$$

The regression sum of squares given in equation (38) can be written, using equations (48) and (50), as

$$(51) \quad SSR = \sum_{k=1}^P (G_k - G_p)^T C^{-1} (G_k - \bar{G}_\bullet) \\ = \sum_{k=1}^P G_k^T C^{-1} G_k - G_\bullet^T C^{-1} G_\bullet / P$$

B. The regression sums of squares assuming some of the parameters to be zero

The term  $G_k^T C^{-1} G_k$  is the regression sum of squares at time  $k$  given in equation (11). As in the model at time  $k$ , one may again fit a reduced model by eliminating the elements in the  $A$  and  $B_{ij}$  vectors that are associated with the parameter effects being omitted. This has the same effect as before, that of eliminating the corresponding elements of the  $G_k$  vector and the corresponding rows and columns of the  $C$  matrix. Using notation consistent with equation (13), define

$$(52) \quad SS(T, AxT, BxT, AxBxT) = \sum_k G_{0k}^T C_0^{-1} G_{0k} - G_0^T C_0^{-1} G_0 / P \\ SS(T, AxT, BxT) = \sum_k G_{1k}^T C_1^{-1} G_{1k} - G_1^T C_1^{-1} G_1 / P \\ SS(T, AxT) = \sum_k G_{2k}^T C_2^{-1} G_{2k} - G_2^T C_2^{-1} G_2 / P \\ SS(T, BxT) = \sum_k G_{3k}^T C_3^{-1} G_{3k} - G_3^T C_3^{-1} G_3 / P \\ SS(T) = \sum_k G_{4k}^T C_4^{-1} G_{4k} - G_4^T C_4^{-1} G_4 / P$$

where the symbols in parenthesis indicate constants fitted; T stands for the  $\{y_k\}$ , AxT for the  $\{\alpha y_{ik}\}$ , BxT for the  $\{\beta y_{jk}\}$ , and AxBxT for the  $\{\alpha\beta y_{ijk}\}$ . The individual terms for the regression sums of squares at time k in the sums of squares of equation (52) are the same as the comparable sums of squares at time k in equation (13). Therefore, equations (14) and (15) can be used to calculate these sums of squares. The sums of squares involving the G vectors summed over time are sums of squares for the average-over-time effects. Four of these can be calculated as

$$(53) \quad G_0^T \cdot C_0^{-1} G_0 \cdot /p = \sum_i \sum_j y_{ij}^2 \cdot /pn_{ij}$$

$$G_2^T \cdot C_2^{-1} G_2 \cdot /p = \sum_i y_{i\dots}^2 \cdot /pn_{i\dots}$$

$$G_3^T \cdot C_3^{-1} G_3 \cdot /p = \sum_j y_{\cdot j \dots}^2 \cdot /pn_{\cdot j \dots}$$

$$G_4^T \cdot C_4^{-1} G_4 \cdot /p = y_{\dots}^2 \cdot /pn_{\dots}$$

The other average-over-time sum of squares,  $G_1^T \cdot C_1^{-1} G_1 \cdot$ , can be calculated using the  $C_1$  and  $G_{1k}$  defined in equation (15). The sums of squares of interest, calculated as differences of sums of squares given in equation (52), are given in Table 9.

### C. The error sum of squares

The sum of squares for error associated with the

Table 9. Analysis of variance for sources with time as a factor

| Source   | df                   | Sum of Squares   |
|----------|----------------------|--|
| Time     | $p-1$                | $\sum_k G_{4k}^T C_4^{-1} G_{4k} - G_4^T \cdot C_4^{-1} G_4 \cdot /p$  |
| AxT      | $(r-1)(p-1)$         | $(\sum_k G_{1k}^T C_1^{-1} G_{1k} - G_1^T \cdot C_1^{-1} G_1 \cdot /p) -$<br>$(\sum_k G_{3k}^T C_3^{-1} G_{3k} - G_3^T \cdot C_3^{-1} G_3 \cdot /p)$ |
| BxT      | $(q-1)(p-1)$         | $(\sum_k G_{1k}^T C_1^{-1} G_{1k} - G_1^T \cdot C_1^{-1} G_1 \cdot /p) -$<br>$(\sum_k G_{2k}^T C_2^{-1} G_{2k} - G_2^T \cdot C_2^{-1} G_2 \cdot /p)$ |
| AxBxT    | $(r-1)(q-1)(p-1)$    | $(\sum_k G_{0k}^T C_0^{-1} G_{0k} - G_0^T \cdot C_0^{-1} G_0 \cdot /p) -$<br>$(\sum_k G_{1k}^T C_1^{-1} G_{1k} - G_1^T \cdot C_1^{-1} G_1 \cdot /p)$ |
| Error(b) | $(n_{..} - rq)(p-1)$ | $\sum_{ijkm} (Y_{ijkm} - \bar{Y}_{ij \cdot m})^2 -$<br>$(\sum_k G_{0k}^T C_0^{-1} G_{0k} - G_0^T \cdot C_0^{-1} G_0 \cdot /p)$                       |

regression sum of squares is given in equation (34), with the parameters replaced by their least square estimates.

This can be written as

$$(54) \quad \text{SSE}(b) = X^T S^{-1} X - \text{SSR}$$

where  $X$  is defined in equation (29),  $S$  in equation (30) and  $\text{SSR}$  in equation (51). From equations (29) and (30),

$$(55) \quad S^{-1} X = \begin{bmatrix} Q^{-1} X_{111} \\ Q^{-1} X_{112} \\ \vdots \\ Q^{-1} X_{rqn_{rq}} \end{bmatrix}$$

where there are  $n_{..}$  sub-vectors of  $p-1$  elements. Then

$$(56) \quad X^T S^{-1} X = \sum_{ijm} X_{ijm}^T Q^{-1} X_{ijm}$$

Using equations (29) and (40),

$$Q^{-1} X_{ijm} = \frac{1}{p} \begin{bmatrix} (p-1)X_{ij1m} - (X_{ij \cdot m} - X_{ij1m}) \\ (p-1)X_{ij2m} - (X_{ij \cdot m} - X_{ij1m}) \\ \vdots \\ (p-1)X_{ijp'm} - (X_{ij \cdot m} - X_{ijp'm}) \end{bmatrix} = \begin{bmatrix} X_{ij1m} - X_{ij \cdot m}/p \\ X_{ij2m} - X_{ij \cdot m}/p \\ \vdots \\ X_{ijp'm} - X_{ij \cdot m}/p \end{bmatrix}$$

$$X_{ijm}^T Q^{-1} X_{ijm} = \sum_{k=1}^{p'} X_{ijkm} (X_{ijkm} - X_{ij \cdot m} / p)$$

Therefore,

$$\begin{aligned} (57) \quad X^T S^{-1} X &= \sum_{ijm} \sum_{k=1}^{p'} X_{ijkm} (X_{ijkm} - X_{ij \cdot m} / p) \\ &= \sum_{ijm} \sum_{k=1}^p (X_{ijkm} - X_{ij \cdot m} / p)^2 \\ &= \sum_{ijkm} (Y_{ijkm} - \bar{Y}_{ij \cdot m})^2 \end{aligned}$$

For a single error term, the SSR in equation (51) should be the regression sum of squares due to fitting all parameter effects in the expectation model (26). This is given as the first listed equation in (52). The SSE(b) can then be written as shown in Table 9. Substituting for equivalent forms from equations (14) and (53) and rearranging terms, the sums of squares in Table 9 can be shown to be equivalent to the sums of squares in which time is a factor in Table 6.

## VII

## DISCUSSION AND SUMMARY

When repeated measurements are made on the same subject, the repeated observations in time may be correlated. Therefore, the assumption of independent observations cannot be made in general. This type of experiment can be considered as a multivariate experiment, considering observations at each time as a separate variate, and assuming the multivariate instead of univariate normal distribution. The correlation structure among successive observations through time can then be incorporated in the covariance matrix of the observation vectors. The covariance structure is assumed the same for all subjects under all treatment conditions. If no further restrictions are imposed on the covariance structure, then some multivariate procedure could be used for testing the effects of time and the interaction of treatment with time.

If one makes the assumptions that the variances for all times are equal and all the correlations are equal, the covariance matrix has the two parameters, variance and correlation coefficient. Then, the expectation model can be written in univariate form with two errors that are functions of the two parameters above. This covariance structure will occur when all lag serial correlations between the errors at different times for a subject are equal. This seems most reasonable when the serial correlations are all zero. Then,

the errors in time for a subject will be independent. The remaining correlation between observations in time will be due to the random subject effect.

For the general multivariate case in which the covariance matrix does not simplify as above, some multivariate two-way disproportionate analysis would appear to be appropriate for a repeated measurements experiment with treatments in a two-way crossed classification with disproportionate cell frequencies. Under the somewhat restrictive assumptions that all variances are equal and all correlations are equal, a univariate analysis is shown in this thesis to be applicable under certain assumptions about the interactions. Also, a relatively simple computational scheme has been proposed for performing the analysis.

The tests obtained are for the three-factor interaction, the two-factor interactions assuming the three-factor interaction zero, and the main effects assuming all interactions zero. The tests separate into two sets (tests of effects averaged over time and tests of effects with time as a factor) which are calculated from variates that are independent from each other. Therefore, assumptions of zero interactions in one set are not required for tests of effects in the other set. This relaxes some of the above assumptions made on the interactions.

The proposed computational scheme requires the inverse of one matrix of order  $r + q - 1$ , where there are  $r$  levels of

one treatment and  $q$  levels of the other treatment. Then some simple matrix multiplications and the calculation of certain standard sums of squares is all that is necessary for the analysis. This procedure is equivalent to the usual method of fitting constants for all of the parameters, but affords simpler computational forms.

The procedure can be extended to the case for which "time" is a factorial arrangement involving two or more factors. This can be seen since the procedure would involve using the average of the observations for each subject over various combinations of the "time" factors for different sets of sums of squares. This has the effect of eliminating all parameters containing the factors over which averages are taken when the usual unweighted constraints are used.

One of the major problems in repeated measurements experiments is incomplete data. Because subjects are frequently the units being measured repeatedly, the human element enters in and increases the likelihood of missing data. If much of the data for a given subject is missing, that subject might be omitted from the experiment on the basis that it offers little information. Otherwise, some missing data technique may be used. Extension of these missing data techniques has not been made for the class of repeated measurement experiments considered here.

Some work has been done on the simpler model (not considering treatments as a factorial arrangement) under

different assumptions regarding the covariance structure. To date, analyses have not been obtained using any restrictions on the covariance structure other than the one assuming equal variance in time and equal correlations in time.

## VIII

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## IX

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## VITA

Richard C. McNee was born in Blairsburg, Iowa, on April 8, 1926. He has a sister and one brother. His family moved to San Antonio, Texas, in June of 1934. In 1943 he graduated from San Antonio Vocational and Technical High School and joined the Navy. Richard received his honorable discharge from the Navy in 1946 and entered Trinity University at San Antonio that same year. In 1950, he received his Bachelor of Science degree with a major in mathematics.

Richard taught seventh and eighth grade mathematics for two years. Then, he obtained a job with Southwest Research Institute in San Antonio, where he worked for two years. In 1955, he obtained a position with the U.S.A.F. School of Aerospace Medicine, where he is presently employed. In the summer of 1957, he was admitted to the graduate school at Virginia Polytechnic Institute to work toward a Master of Science degree in statistics. After attending four Southern Regional Graduate Summer Sessions, Richard was admitted to Virginia Polytechnic Institute as a full-time student in January, 1966. He plans to receive his M.S. degree in statistics in June, 1966. Richard and his wife, Doris, were married in 1948 and have two daughters, thirteen and eight.

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## ABSTRACT

In experiments with repeated measurements made on the same subjects, the repeated observations in time may be correlated. Therefore, the assumption of independent observations cannot be made in general. This thesis considers the experimental design with treatments in a two-way classification with a disproportionate number of subjects allocated to each treatment combination and repeated measurements made on the subjects.

A procedure is shown to be applicable for computing an analysis under somewhat restrictive assumptions. It is assumed that the variances are equal for all times and the correlations in time are equal. The tests obtained are for the three-factor interaction, the two-factor interactions assuming the three-factor interaction zero, and the main effects assuming all interactions zero. The procedure requires the inverse of one matrix, some matrix multiplication, and the calculation of some standard sums of squares.