5 Univariate repeated measures analysis of variance

5.1 Introduction

As we will see as we progress, there are a number of approaches for representing longitudinal data in terms of a **statistical model**. Associated with these approaches are appropriate methods of analysis that focus on questions that are of interest in the context of longitudinal data. As noted previously, one way to make distinctions among these models and methods has to do with what they assume about the **covariance structure** of a data vector from an unit. Another has to do with what is assumed about the form of the mean of an observation and thus the **mean vector** for a data vector.

We begin our investigation of the different models and methods by considering a particular statistical model for representing longitudinal data. This model is really only applicable in the case where the data are **balanced**; that is, where the measurements on each unit occur at the same n times for all units, with no departures from these times or missing values for any units. Thus, each individual has associated an n-dimensional random vector, whose jth element corresponds to the response at the jth (common) time point.

Although, as we will observe, the model may be put into the general form discussed in Chapters 3 and 4, where we think of the data in terms of vectors for each individual and the means and covariances of these vectors, it is motivated by considering a model for **each individual observation** separately. Because of this motivation, the model and the associated method of analysis is referred to as **univariate** repeated measures analysis of variance.

- This model imposes a very specific assumption about the covariances of the data vectors, one that may often not be fulfilled for longitudinal data.
- Thus, because the method exploits this possibly incorrect assumption, there is the potential for erroneous inferences in the case that the assumption made is not relevant for the data at hand.
- The model also provides a simplistic representation for the mean of a data vector that does not exploit the fact that each vector represents what might appear to be a systematic **trajectory** that appears to be a **function** of time (recall the examples in Chapter 1 and the sample mean vectors for the dental data in the last chapter).

- However, because of its simplicity and connection to familiar analysis of variance techniques, the model and method are quite popular, and are often adopted by default, sometimes without proper attention to the validity of the assumptions.

We will first describe the model in the way it is usually represented, which will involve slightly different notation than that we have discussed. This notation is conventional in this setting, so we begin by using it. We will then make the connection between this representation and the way we have discussed thinking about longitudinal data, as vectors.

5.2 Basic situation and statistical model

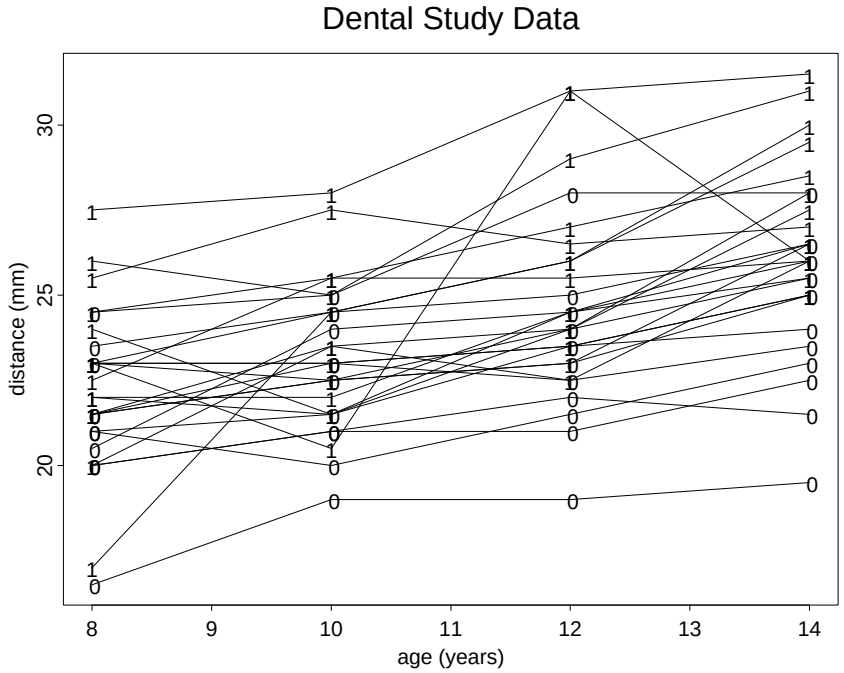
Recall Examples 1 and 2 in Chapter 1:

- In Example 1, the dental study, 27 children, 16 boys and 11 girls, were observed at each of ages 8, 10, 12, and 14 years. At each time, the response, a measurement of the distance from the center of the pituitary to the pterygomaxillary fissure was made. Objectives were to learn whether there is a difference between boys and girls with respect to this measure and its change over time.
- In Example 2, the diet study, 15 guinea pigs were randomized to receive zero, low, or high dose of a vitamin E diet supplement. Body weight was measured at each of several time points (weeks 1, 3, 4, 5, 6, and 7) for each pig. Objectives were to determine whether there is a difference among pigs treated with different doses of the supplement with respect to body weight and its change over time.

Recall from Figures 1 and 2 of Chapter 1 that, each child or guinea pig exhibited a **profile** over time (age or weeks) that appeared to increase with time; Figure 1 of Chapter 1 is reproduced in Figure 1 here for convenience.

In these examples, the response of interest is **continuous** (distance, body weight).

Figure 1: *Orthodontic distance measurements (mm) for 27 children over ages 8, 10, 12, 14. The plotting symbols are 0's for girls, 1's for boys.*



STANDARD SETUP: These situations typify the usual setup of a standard (one-way) longitudinal or repeated measurement study.

- Units are randomized to one of $q \geq 1$ **treatment groups**. In the literature, these are often referred to as the **between-units** factors or groups. (This is an abuse of grammar if the number of groups is greater than 2; **among-units** would be better.) In the dental study, $q = 2$, boys and girls (where randomly selecting boys from the population of all boys and similarly for girls is akin to randomization of units). In the diet study, we think of $q = 3$ dose groups.

- The response of interest is measured on each of n occasions or under each of n conditions. Although in a longitudinal study, this is usually "time," it may also be something else. For example, suppose men were randomized into two groups, regular and modified diet. The repeated responses might be maximum heart rate measurements after separate occasions of 10, 20, 30, 45, and 60 minutes walking on a treadmill. As is customary, we will refer to the repeated measurement factor as **time** with the understanding that it might apply equally well to thing other than strictly chronological "time." It is often also referred to in the literature as the **within-units** factor. In the dental study, this is age ($n = 4$); in the diet study, weeks ($n = 6$).

- For simplicity, we will consider in detail the case where there is a single factor making up the groups (e.g. gender, dose); however, it is straightforward to extend the development to the case where the groups are determined by a **factorial design**; e.g. if in the diet study there had been $q = 6$ groups, determined by the factorial arrangement of 3 doses and 2 genders.

SOURCES OF VARIATION: As discussed in Chapter 4, the model recognizes two possible **sources of variation** that may make observations on units in the same group taken at the same time differ:

- There is random variation in the population of units due to, for example, biological variation. For example, if we think of the population of all possible guinea pigs if they were all given the low dose, they would produce different responses at week 1 simply because guinea pigs vary biologically and are not all identical.

  We may thus identify random variation **among individuals (units)**.

- There is also random variation due to **within-unit fluctuations** and **measurement error**, as discussed in Chapter4.

  We may thus identify random variation **within individuals (units)**.

It is important that any statistical model take these two sources of variation into appropriate account. Clearly, these sources will play a role in determining the nature of the covariance matrix of a data vector; we will see this for the particular model we now discuss in a moment.

MODEL: To state the model in the usual way, we will use notation different from that we have discussed so far. We will then show how the model in the standard notation may also be represented as we have discussed. Define the random variable

$$Y_{h\ell j} = \text{observation on unit } h \text{ in the } \ell\text{th group at time } j.$$

- $h = 1, \ldots, r_\ell$, where r_ℓ denotes the number of units in group ℓ. Thus, in this notation, h indexes units **within** a particular group.
- $\ell = 1, \ldots, q$ indexes groups
- $j = 1, \ldots, n$ indexes the levels of time

- Thus, the total number of units involved is $m = \sum_{\ell=1}^{q} r_\ell$. Each is observed at n time points.

The model for $Y_{h\ell j}$ is given by

$$Y_{h\ell j} = \mu + \tau_\ell + b_{h\ell} + \gamma_j + (\tau\gamma)_{\ell j} + e_{h\ell j} \tag{5.1}$$

- μ is an "overall mean"
- τ_ℓ is the deviation from the overall mean associated with being in group ℓ
- γ_j is the deviation associated with time j
- $(\tau\gamma)_{\ell j}$ is an additional deviation associated with group ℓ and time j; $(\tau\gamma)_{\ell j}$ is the **interaction** effect for group ℓ, time j
- $b_{h\ell}$ is a **random effect** with $E(b_{h\ell}) = 0$ representing the deviation caused by the fact that $Y_{h\ell j}$ is measured on the hth particular unit in the ℓth group. That is, responses vary because of random variation **among** units. If we think of the population of all possible units were they to receive the treatment of group ℓ, we may think of each unit as having its own deviation simply because it differs biologically from other units. Formally, we may think of this population as being represented by a **probability distribution** of all possible $b_{h\ell}$ values, one per unit in the population. $b_{h\ell}$ thus characterizes the source of random variation due to **among-unit** causes. The term **random effect** is customary to describe a model component that addresses **among-unit** variation.
- $e_{h\ell j}$ is a **random deviation** with $E(e_{h\ell j}) = 0$ representing the deviation caused by the aggregate effect of within-unit fluctuations and measurement error (**within-unit** sources of variation). That is, responses also vary because of variation **within** units. Recalling the model in Chapter 4, if we think of the population of all possible combinations of fluctuations and measurement errors that might happen, we may represent this population by a **probability distribution** of all possible $e_{h\ell j}$ values. The term "**random error**" is usually used to describe this model component, but, as we have remarked previously, we prefer **random deviation**, as this effect may be due to more than just measurement error.

REMARKS:

- Model (5.1) has exactly the same form as the statistical model for observations arising from an experiment conducted according to a **split plot** design. Thus, as we will see, the analysis is identical; however, the interpretation and further analyses are different.

- Note that the **actual values** of the times of measurement (e.g. ages 8, 10, 12, 14 in the dental study) **do not** appear explicitly in the model. Rather, a separate deviation parameter γ_j and and interaction parameter $(\tau\gamma)_{\ell j}$ is associated with each time. Thus, the model takes no explicit account of where the times of observation are chronologically; e.g. are they equally-spaced?

MEAN MODEL: The model (5.1) represents how we believe **systematic** factors like time and treatment (group) and **random variation** due to various sources may affect the way a response turns out. To exhibit this more clearly, it is instructive to re-express the model as

$$Y_{h\ell j} = \underbrace{\mu + \tau_\ell + \gamma_j + (\tau\gamma)_{\ell j}}_{\mu_{\ell j}} + \underbrace{b_{h\ell} + e_{h\ell j}}_{\epsilon_{h\ell j}} \tag{5.2}$$

- Because $b_{h\ell}$ and $e_{h\ell j}$ have mean 0, we have of course

$$E(Y_{h\ell j}) = \mu_{\ell j} = \mu + \tau_\ell + \gamma_j + (\tau\gamma)_{\ell j}.$$

  Thus, $\mu_{\ell j} = \mu+\tau_\ell+\gamma_j+(\tau\gamma)_{\ell j}$ represents the mean for a unit in the ℓth group at the jth observation time. This mean is the sum of deviations from an overall mean caused by a fixed systematic effect on the mean due to group ℓ that happens at all time points (τ_ℓ), a fixed systematic effect on the mean that happens regardless of group at time j (γ_j), and an additional fixed systematic effect on the mean that occurs for group ℓ at time j ($(\tau\gamma)_{\ell j}$).

- $\epsilon_{h\ell j} = b_{h\ell} + e_{h\ell j}$ the sum of random deviations that cause $Y_{h\ell j}$ to differ from the mean at time j for the hth unit in group ℓ. $\epsilon_{h\ell j}$ summarizes all sources **random variation**.

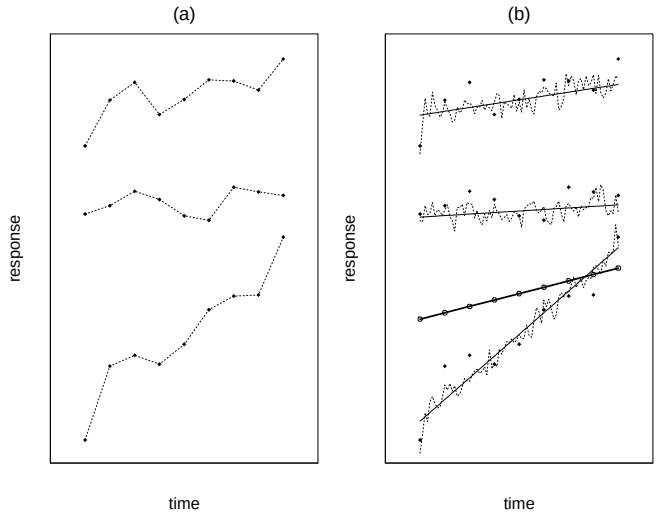
- Note that $b_{h\ell}$ does not have a subscript "j." Thus, the deviation that "places" the hth unit in group ℓ in the population of all such units relative to the mean response is **the same** for all time points. This represents an **assumption**: if a unit is "high" at time j relative to the group mean at j, it is "high" by the same amount at all other times.

  This may or not be reasonable. For example, recall Figure 1 in Chapter 4, reproduced here as Figure 2.

This assumption might be reasonable for the upper two units in panel (b), as the "inherent trends" for these units are roughly parallel to the trajectory of means over time. But the lower unit's trend is far below the mean at early times but rises to be above it at later times; for this unit, the deviation from the mean is not the same at all times.

As we will see shortly, violation of this assumption may not be critical as long as the overall pattern of variance and correlation implied by this model is similar to that in the data.

Figure 2: *(a) Hypothetical longitudinal data from $m = 3$ units at $n = 9$ time points. (b) Conceptual representation of sources of variation.*



NORMALITY AND VARIANCE ASSUMPTIONS: For continuous responses like those in the example, it is often realistic to consider the **normal distribution** as a model for the way in which the various sources of variation affect the response. If $Y_{h\ell j}$ is continuous, we would expect that the deviations due to biological variation (among-units) and within-unit sources that affect how $Y_{h\ell j}$ turns out to also be continuous. Thus, rather than assuming that $Y_{h\ell j}$ is normally distributed directly, it is customary to assume that each random component arises from a normal distribution.

Specifically, the standard assumptions, which also incorporate assumptions about variance, are:

- $b_{h\ell} \sim \mathcal{N}(0, \sigma_b^2)$ and are all independent. This says that the distribution of deviations in the population of units is centered about 0 (some are negative, some positive), with variation characterized by the **variance component** σ_b^2.

The fact that this normal distribution is identical for all $\ell = 1, \ldots, q$ reflects an assumption that units vary similarly among themselves in all q populations. The independence assumption represents the reasonable view that the response one unit in the population gives at any time is completely unrelated to that given by another unit.

- $e_{h\ell j} \sim \mathcal{N}(0, \sigma_e^2)$ and are all independent. This says that the distribution of deviations due to **within-unit** causes is centered about 0 (some negative, some positive), with variation characterized by the (common) **variance component** σ_e^2.

  That this distribution is the **same** for all $\ell = 1, \ldots, q$ and $j = 1, \ldots, n$ again is an **assumption**. The variance σ_e^2 represents the "aggregate" variance of the combined fluctuation and measurement error processes, and is assumed to be **constant** over time and group. Thus, the model assumes that the combined effect of within-unit sources of variation is the **same** at any time in all groups. E.g. the magnitude of within-unit fluctuations is similar across groups and does not change with time, and the variability associated with errors in measurement is the same regardless of the size of the thing being measured.

  The independence assumption is something we must think about carefully. It is customary to assume that the error in measurement introduced by, say, an imperfect scale at one time point is not related to the error in measurement that occurs at a later time point; i.e. measurement errors occur "haphazardly." Thus, if $e_{h\ell j}$ represents mostly measurement error, the independence assumption seems reasonable. However, fluctuations within a unit may well be **correlated**, as discussed in the last chapter. Thus, if the time points are close enough together so that correlations are not negligible, this may not be reasonable. (recall our discussion of observations close in time tending to be "large" or "small" together).

- The $b_{h\ell}$ and $e_{h\ell j}$ are assumed to all be mutually independent. This represents the view that deviations due to within-unit sources are of similar magnitude regardless of the the magnitudes of the deviations $b_{h\ell}$ associated with the units on which the observations are made. This is often reasonable; however, as we will see later in the course, there are certain situations where it may not be reasonable.

With these assumptions it will follow that the $Y_{h\ell j}$s are normally distributed, as we will now demonstrate.

VECTOR REPRESENTATION AND COVARIANCE MATRIX: Now consider the data on a particular unit. With this notation, the subscripts h and ℓ identify a particular unit as the hth unit in the ℓth group.

For this unit, we may summarize the observations at the n times in a vector and write

$$\begin{pmatrix} Y_{h\ell 1} \\ Y_{h\ell 2} \\ \vdots \\ Y_{h\ell n} \end{pmatrix} = \begin{pmatrix} \mu + \tau_\ell + \gamma_1 + (\tau\gamma)_{\ell 1} \\ \mu + \tau_\ell + \gamma_2 + (\tau\gamma)_{\ell 2} \\ \vdots \\ \mu + \tau_\ell + \gamma_n + (\tau\gamma)_{\ell n} \end{pmatrix} + \begin{pmatrix} b_{h\ell} \\ b_{h\ell} \\ \vdots \\ b_{h\ell} \end{pmatrix} + \begin{pmatrix} e_{h\ell 1} \\ e_{h\ell 2} \\ \vdots \\ e_{h\ell n} \end{pmatrix} \tag{5.3}$$

$$\boldsymbol{Y}_{h\ell} = \boldsymbol{\mu}_\ell + \mathbf{1}b_{h\ell} + \boldsymbol{e}_{h\ell},$$

where $\mathbf{1}$ is a $(n \times 1)$ vector of 1s, or more succinctly,

$$\begin{pmatrix} Y_{h\ell 1} \\ Y_{h\ell 2} \\ \vdots \\ Y_{h\ell n} \end{pmatrix} = \begin{pmatrix} \mu_{\ell 1} \\ \mu_{\ell 2} \\ \vdots \\ \mu_{\ell n} \end{pmatrix} + \begin{pmatrix} \epsilon_{h\ell 1} \\ \epsilon_{h\ell 2} \\ \vdots \\ \epsilon_{h\ell n} \end{pmatrix} \tag{5.4}$$

$$\boldsymbol{Y}_{h\ell} = \boldsymbol{\mu}_\ell + \boldsymbol{\epsilon}_{h\ell},$$

so, for the data vector from the hth unit in group ℓ,

$$E(\boldsymbol{Y}_{h\ell}) = \boldsymbol{\mu}_\ell.$$

We see that the model implies a very specific representation of a data vector. Note that for all units from the same group (ℓ) $\boldsymbol{\mu}_\ell$ is the same.

We will now see that the model implies something very specific about how observations within and across units **covary** and about the structure of the mean of a data vector.

- Because $b_{h\ell}$ and $e_{h\ell j}$ are independent, we have

$$\text{var}(Y_{h\ell j}) = \text{var}(b_{h\ell}) + \text{var}(e_{h\ell j}) + 2\text{cov}(b_{h\ell}, e_{h\ell j}) = \sigma_b^2 + \sigma_e^2 + 0 = \sigma_b^2 + \sigma_e^2.$$

- Furthermore, because each random component $b_{h\ell}$ and $e_{h\ell j}$ is normally distributed, each $Y_{h\ell j}$ is normally distributed.

- In fact, the $Y_{h\ell j}$ values making up the vector $\boldsymbol{Y}_{h\ell}$ are jointly normally distributed.

Thus, a data vector $\boldsymbol{Y}_{h\ell}$ under the assumptions of this model has a multivariate (n-dimensional) normal distribution with mean vector $\boldsymbol{\mu}_\ell$. We now turn to the form of the covariance matrix of $\boldsymbol{Y}_{h\ell}$.

FACT: First we note the following result. If b and e are two random variables with means μ_b and μ_e, then $\text{cov}(b, e) = 0$ implies that $E(be) = E(b)E(e) = \mu_b\mu_e$. This is shown as follows:

$$\text{cov}(b, e) = E(b - \mu_b)(e - \mu_e) = E(be) - E(b)\mu_e - \mu_b E(e) + \mu_b\mu_e = E(be) - \mu_b\mu_e.$$

Thus, $\text{cov}(b, e) = 0 = E(be) - \mu_b\mu_e$, and the result follows.

- We know that if b and e are jointly normally distributed and independent, then $\text{cov}(b, e) = 0$.
- Thus, b and e independent and normal implies $E(be) = \mu_b\mu_e$. If furthermore b and e have means 0, i.e. $E(b) = 0$, $E(e) = 0$, then in fact
$$E(be) = 0.$$

We now use this result to examine the covariances.

- First, let $Y_{h\ell j}$ and $Y_{h'\ell' j'}$ be two observations taken from different units (h and h') from different groups (ℓ and ℓ') at different times (j and j').

$$\begin{aligned} \text{cov}(Y_{h\ell j}, Y_{h'\ell' j'}) &= E(Y_{h\ell j} - \mu_{\ell j})(Y_{h'\ell' j'} - \mu_{\ell' j'}) = E(b_{h\ell} + e_{h\ell j})(b_{h'\ell'} + e_{h'\ell' j'}) \\ &= E(b_{h\ell}b_{h'\ell'}) + E(e_{h\ell j}b_{h'\ell'}) + E(b_{h\ell}e_{h'\ell' j'}) + E(e_{h\ell j}e_{h'\ell' j'}) \qquad (5.5) \end{aligned}$$

  Note that, since all the random components are assumed to be **mutually independent** with 0 means, by the above result, we have that each term in (5.5) is equal to 0! Thus, (5.5) implies that two responses from different units in different groups at different times are not correlated.

- In fact, the same argument goes through if $\ell = \ell'$, i.e. the observations are from two different units in the same group and/or $j = j'$, i.e. the observations are from two different units at the same time. That is (try it!),

$$\text{cov}(Y_{h\ell j}, Y_{h'\ell j'}) = 0, \quad \text{cov}(Y_{h\ell j}, Y_{h'\ell' j}) = 0, \quad \text{cov}(Y_{h\ell j}, Y_{h'\ell j}) = 0.$$

- Thus, we may conclude that the model (5.1) **automatically** implies that **any two** observations from **different** units have 0 covariance. Furthermore, because these observations are all normally distributed, this implies that any two observations from different units are **independent**! Thus, two **vectors** $\boldsymbol{Y}_{h\ell}$ and $\boldsymbol{Y}_{h'\ell'}$ from different units, where $\ell \neq \ell'$ or $\ell = \ell'$, are **independent** under this model!

  Recall that at the end of Chapter 3, we noted that it seems reasonable to assume that data vectors from different units are indeed **independent**; this model **automatically** induces this assumption.

- Now consider 2 observations on the **same** unit, say the hth unit in group ℓ, $Y_{h\ell j}$ and $Y_{h\ell j'}$. We have

$$\begin{aligned} \text{cov}(Y_{h\ell j}, Y_{h\ell j'}) &= E(Y_{h\ell j} - \mu_{\ell j})(Y_{h\ell j'} - \mu_{\ell j'}) = E(b_{h\ell} + e_{h\ell j})(b_{h\ell} + e_{h\ell j'}) \\ &= E(b_{h\ell}b_{h\ell}) + E(e_{h\ell j}b_{h\ell}) + E(b_{h\ell}e_{h\ell j'}) + E(e_{h\ell j}e_{h\ell j'}) \\ &= \sigma_b^2 + 0 + 0 + 0 = \sigma_b^2. \end{aligned} \tag{5.6}$$

  This follows because all of the random variables in the last three terms are mutually independent according to the assumptions and

$$E(b_{h\ell}b_{h\ell}) = E(b_{h\ell} - 0)^2 = \text{var}(b_{h\ell}) = \sigma_b^2$$

  by the assumptions.

COVARIANCE MATRIX: Summarizing this information in the form of a covariance matrix, we see that

$$\text{var}(\boldsymbol{Y}_{h\ell}) = \begin{pmatrix} \sigma_b^2 + \sigma_e^2 & \sigma_b^2 & \cdots & \sigma_b^2 \\ \sigma_b^2 & \sigma_b^2 + \sigma_e^2 & \cdots & \sigma_b^2 \\ \vdots & \vdots & \vdots & \vdots \\ \sigma_b^2 & \sigma_b^2 & \cdots & \sigma_b^2 + \sigma_e^2 \end{pmatrix} \tag{5.7}$$

- Actually, we could have obtained this matrix more directly by using matrix operations applied to the matrix form of (5.3). Specifically, because $b_{h\ell}$ and the elements of $\boldsymbol{e}_{h\ell}$ are independent and normal, $\mathbf{1}b_{h\ell}$ and $\boldsymbol{e}_{h\ell}$ are independent, multivariate normal random vectors,

$$\text{var}(\boldsymbol{Y}_{h\ell}) = \text{var}(\mathbf{1}b_{h\ell}) + \text{var}(\boldsymbol{e}_{h\ell}) = \mathbf{1}\text{var}(b_{h\ell})\mathbf{1}' + \text{var}(\boldsymbol{e}_{h\ell}). \tag{5.8}$$

  Now $\text{var}(b_{h\ell}) = \sigma_b^2$. Furthermore (try it),

$$\mathbf{1}\mathbf{1}' = \boldsymbol{J}_n = \begin{pmatrix} 1 & \cdots & 1 \\ 1 & \cdots & 1 \\ \vdots & \vdots & \vdots \\ 1 & \cdots & 1 \end{pmatrix} \text{ and } \text{var}(\boldsymbol{e}_{h\ell}) = \sigma_e^2\boldsymbol{I}_n;$$

  applying these to (5.8) gives

$$\text{var}(\boldsymbol{Y}_{h\ell}) = \sigma_b^2\boldsymbol{J}_n + \sigma_e^2\boldsymbol{I}_n = \boldsymbol{\Sigma}. \tag{5.9}$$

  It is straightforward to observe by writing out (5.9) in detail that it is just a compact way, in matrix notation, to state (5.7).

- It is customary to use $\boldsymbol{J}$ to denote a square matrix of all 1s, where we add the subscript when we wish to emphasize the dimension.

- We thus see that we may summarize the assumptions of model (5.1) in matrix form: The m data vectors $\boldsymbol{Y}_{h\ell}$, $h = 1, \ldots, r_\ell$, $\ell = 1, \ldots, q$ are all independent and multivariate normal with

$$\boldsymbol{Y}_{h\ell} \sim \mathcal{N}_n(\boldsymbol{\mu}_\ell, \boldsymbol{\Sigma}),$$

  where $\boldsymbol{\Sigma}$ is given in (5.9).

COMPOUND SYMMETRY: We thus see from given in (5.7) and (5.9) is that this model assumes that the covariance of a random data vector has the **compound symmetry** or **exchangeable** correlation structure (see Chapter 4).

- Note that the off-diagonal elements of this matrix (the covariances among elements of $\boldsymbol{Y}_{h\ell}$) are equal to σ_b^2. Thus, if we compute the correlations, they are all the same and equal to (verify) $\sigma_b^2/(\sigma_b^2 + \sigma_e^2)$. This is called the **intra-class correlation** in some contexts.

- As we noted earlier, this model says that no matter how far apart or near in time two elements of $\boldsymbol{Y}_{h\ell}$ were taken, the degree of association between them is **the same**. Hence, with respect to association, they are essentially interchangeable (or **exchangeable**).

- Moreover, the association is **positive**; i.e. because both σ_b^2 and σ_e^2 are **variances**, both are positive. Thus, the correlation, which depends on these two positive quantities, must also be positive.

- The diagonal elements of are also all the **same**, implying that the variance of each element of $\boldsymbol{Y}_{h\ell}$ is the same.

- This covariance structure is a special case of something called a **Type H** covariance structure. More on this later.

- As we have noted previously, the compound symmetric structure may be a rather restrictive assumption for longitudinal data, as it tends to emphasize **among-unit** sources of variation. If the within-unit source of correlation (due to fluctuations) is non-negligible, this may be a poor representation. Thus, assuming the model (5.1) implies this fairly restrictive assumption on the nature of variation within a data vector.

- The implied covariance matrix (5.7) is the **same** for all units, regardless of group.

As we mentioned earlier, using model (5.1) as the basis for analyzing longitudinal data is quite common but may be inappropriate. We now see why – the model implies a restrictive and possibly unrealistic assumption about correlation among observations on the same unit over time!

ALTERNATIVE NOTATION: We may in fact write the model in our previous notation. Note that h indexes units **within** groups, and ℓ indexes groups, for a total of $m = \sum_{\ell=1}^{q} r_\ell$ units. We could thus **reindex** units by a **single index**, $i = 1, \ldots, m$, where the value of i for any given unit is determined by its (unique) values of h and ℓ. We could reindex $b_{h\ell}$ and $\boldsymbol{e}_{h\ell}$ in the same way. Thus, let $\boldsymbol{Y}_i$, $i = 1, \ldots, m$, i.e.

$$\boldsymbol{Y}_i = \begin{pmatrix} Y_{i1} \\ \vdots \\ Y_{in} \end{pmatrix},$$

denote the vectors $\boldsymbol{Y}_{h\ell}$, $h = 1, \ldots, r_\ell$, $\ell = 1, \ldots, q$ reindexed, and similarly write b_i and $\boldsymbol{e}_i$. To express the model with this indexing, the information on group membership must somehow be incorporated separately, as it is no longer explicit from the indexing. To do this, it is common to write the model as follows.

Let $\boldsymbol{M}$ denote the matrix of all means $\mu_{\ell j}$ implied by the model (5.1), i.e.

$$\boldsymbol{M} = \begin{pmatrix} \mu_{11} & \mu_{12} & \cdots & \mu_{1n} \\ \vdots & \vdots & \vdots & \vdots \\ \mu_{q1} & \mu_{q2} & \cdots & \mu_{qn} \end{pmatrix}. \tag{5.10}$$

The ℓth row of the matrix $\boldsymbol{M}$ in (5.10) is thus the transpose of the mean vector $\boldsymbol{\mu}_\ell$ $(n \times 1)$, i.e.

$$\boldsymbol{M} = \begin{pmatrix} \boldsymbol{\mu}_1' \\ \vdots \\ \boldsymbol{\mu}_q' \end{pmatrix}.$$

Also, using the new indexing system, let, for $\ell = 1, \ldots, q$,

$$\begin{aligned} a_{i\ell} &= 1 \text{ if unit } i \text{ is from group } \ell \\ &= 0 \text{ otherwise} \end{aligned}$$

Thus, the $a_{i\ell}$ record the information on group membership. Now let $\boldsymbol{a}_i$ be the vector $(q \times 1)$ of $a_{i\ell}$ values corresponding to the ith unit, i.e.

$$\boldsymbol{a}_i' = (a_{i1}, a_{i2}, \ldots, a_{iq});$$

because any unit may only belong to one group, $\boldsymbol{a}_i$ will be a vector of all 0s except for a 1 in the position corresponding to i's group. For example, if there are $q = 3$ groups and $n = 4$ times, then

$$\boldsymbol{M} = \begin{pmatrix} \mu_{11} & \mu_{12} & \mu_{13} & \mu_{14} \\ \mu_{21} & \mu_{22} & \mu_{23} & \mu_{24} \\ \mu_{31} & \mu_{32} & \mu_{33} & \mu_{34} \end{pmatrix}$$

and if the ith unit is from group 2, then

$$\boldsymbol{a}_i' = (0, 1, 0),$$

so that (verify)

$$\boldsymbol{a}_i'\boldsymbol{M} = (\mu_{21}, \mu_{22}, \mu_{23}, \mu_{24}) = \boldsymbol{\mu}_i',$$

say, the mean vector for the ith unit. The particular elements of $\boldsymbol{\mu}_i$ are determined by the group membership of unit i, and are the same for all units in the same group.

Using these definitions, it is straightforward (try it) to verify that we may rewrite the model in (5.3) and (5.4) as

$$\boldsymbol{Y}_i' = \boldsymbol{a}_i'\boldsymbol{M} + \boldsymbol{1}'b_i + \boldsymbol{e}_i', \quad i = 1, \ldots, m.$$

and

$$\boldsymbol{Y}_i' = \boldsymbol{a}_i'\boldsymbol{M} + \boldsymbol{\epsilon}_i', \quad i = 1, \ldots, m. \tag{5.11}$$

This one standard way of writing the model when indexing units is done with a single subscript (i in this case).

In particular, this way of writing the model is used in the documentation for SAS `PROC GLM`. The convention is to put the model "on its side," which can be confusing.

Another way of writing the model that is more familiar and more germane to our later development is as follows. Let $\boldsymbol{\beta}$ be the vector of all parameters in the model (5.1) for all groups and times; i.e. all of μ, the τ_ℓ, γ_j, and $(\tau\gamma)_{\ell j}$, $\ell = 1, \ldots, q$, $j = 1, \ldots, n$. For example, with $q = 2$ groups and $n = 3$ time points,

$$\boldsymbol{\beta} = \begin{pmatrix} \mu \\ \tau_1 \\ \tau_2 \\ \gamma_1 \\ \gamma_2 \\ \gamma_3 \\ (\tau\gamma)_{11} \\ (\tau\gamma)_{12} \\ (\tau\gamma)_{13} \\ (\tau\gamma)_{21} \\ (\tau\gamma)_{22} \\ (\tau\gamma)_{23} \end{pmatrix}.$$

Now $E(\boldsymbol{Y}_i) = \boldsymbol{\mu}_i$. If, for example, i is in group 2, then

$$\boldsymbol{\mu}_i = \begin{pmatrix} \mu_{21} \\ \mu_{22} \\ \mu_{23} \end{pmatrix} = \begin{pmatrix} \mu + \tau_2 + \gamma_1 + (\tau\gamma)_{21} \\ \mu + \tau_2 + \gamma_2 + (\tau\gamma)_{22} \\ \mu + \tau_2 + \gamma_3 + (\tau\gamma)_{23} \end{pmatrix}.$$

Note that if we define

$$\boldsymbol{X}_i = \left(\begin{array}{c|cc|ccc|ccc|cc} 1 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 1 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 1 & 0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 1 \end{array}\right),$$

then (verify), we can write

$$\boldsymbol{\mu}_i = \boldsymbol{X}_i\boldsymbol{\beta}.$$

Thus, in any general model, we see that, if we define $\boldsymbol{\beta}$ and $\boldsymbol{X}_i$ appropriately, we can write the model as

$$\boldsymbol{Y}_i = \boldsymbol{X}_i\boldsymbol{\beta} + \mathbf{1}b_i + \boldsymbol{e}_i \quad \text{or} \quad \boldsymbol{Y}_i = \boldsymbol{X}_i\boldsymbol{\beta} + \boldsymbol{\epsilon}_i, \quad i = 1, \ldots, m.$$

$\boldsymbol{X}_i$ would be the appropriate matrix of 0s and 1s, and would be the same for each i in the same group.

PARAMETERIZATION: Just as with any model of this type, we note that representing the means $\mu_{\ell j}$ in terms of parameters μ, τ_ℓ, γ_j, and $(\tau\gamma)_{\ell j}$ leads to a model that is **overparameterized**. That is, while we do have enough information to figure out how the means $\mu_{\ell j}$ differ, we do not have enough information to figure out how they break down into all of these components. For example, if we had 2 treatment groups, we can't tell where all of μ, τ_1, and τ_2 ought to be just from the information at hand. To see what we mean, suppose we knew that $\mu + \tau_1 = 20$ and $\mu + \tau_2 = 10$. Then one way this could happen is if

$$\mu = 15, \quad , \tau_1 = 5, \quad \tau_2 = -5;$$

another way is

$$\mu = 12, \quad , \tau_1 = 8, \quad \tau_2 = -2;$$

in fact, we could write zillions of more ways. Equivalently, this issue may also be seen by realizing that the matrix $\boldsymbol{X}_i$ is **not of full rank**.

Thus, the point is that, although this type of representation of a mean $\mu_{\ell j}$ used in the context of analysis of variance is convenient for helping us think about effects of different factors as deviations from an "overall" mean, we can't identify all of these components. In order to identify them, it is customary to impose **constraints** that make the representation unique by forcing only one of the possible zillions of ways to hold:

$$\sum_{\ell=1}^{q} \tau_\ell = 0, \quad \sum_{j=1}^{n} \gamma_j = 0, \quad \sum_{\ell=1}^{q} (\tau\gamma)_{\ell j} = 0 = \sum_{j=1}^{n} (\tau\gamma)_{\ell j} \text{ for all } j, \ell.$$

Imposing these constraints is equivalent to redefining the vector of parameters $\boldsymbol{\beta}$ and the matrices $\boldsymbol{X}_i$ so that $\boldsymbol{X}_i$ will always be a **full rank** matrix for all i.

REGRESSION INTERPRETATION: The interesting feature of this representation is that it looks like we have a set of m "regression" models, indexed by i, each with its own "design matrix" $\boldsymbol{X}_i$ and "deviations" $\boldsymbol{\epsilon}_i$. We will see later that more flexible models for repeated measurements are also of this form; thus, writing (5.1) this way will allow us to compare different models and methods directly.

Regardless of how we write the model, it is important to remember that an important assumption of the model is that all data vectors are multivariate normal with the **same** covariance matrix having a very specific form; i.e. with this indexing, we have

$$\boldsymbol{Y}_i \sim \mathcal{N}_n(\boldsymbol{\mu}_i, \boldsymbol{\Sigma}), \quad \boldsymbol{\Sigma} = \sigma_b^2 \boldsymbol{J}_n + \sigma_e^2 \boldsymbol{I}_n.$$

5.3 Questions of interest and statistical hypotheses

We now focus on how questions of scientific interest may be addressed in the context of such a model for longitudinal data. Recall that we may write the model as in (5.11), i.e.

$$\boldsymbol{Y}_i' = \boldsymbol{a}_i'\boldsymbol{M} + \boldsymbol{\epsilon}_i', \quad i = 1, \ldots, m, \tag{5.12}$$

where

$$\boldsymbol{M} = \begin{pmatrix} \mu_{11} & \mu_{12} & \cdots & \mu_{1n} \\ \vdots & \vdots & \vdots & \vdots \\ \mu_{q1} & \mu_{q2} & \cdots & \mu_{qn} \end{pmatrix}$$

and

$$\mu_{\ell j} = \mu + \tau_\ell + \gamma_j + (\tau\gamma)_{\ell j}. \tag{5.13}$$

The constraints

$$\sum_{\ell=1}^{q} \tau_\ell = 0, \quad \sum_{j=1}^{n} \gamma_j = 0, \quad \sum_{\ell=1}^{q} (\tau\gamma)_{\ell j} = 0 = \sum_{j=1}^{n} (\tau\gamma)_{\ell j}$$

are assumed to hold.

The model (5.12) is sometimes written succinctly as

$$\boldsymbol{\mathcal{Y}} = \boldsymbol{A}\boldsymbol{M} + \boldsymbol{\epsilon}, \tag{5.14}$$

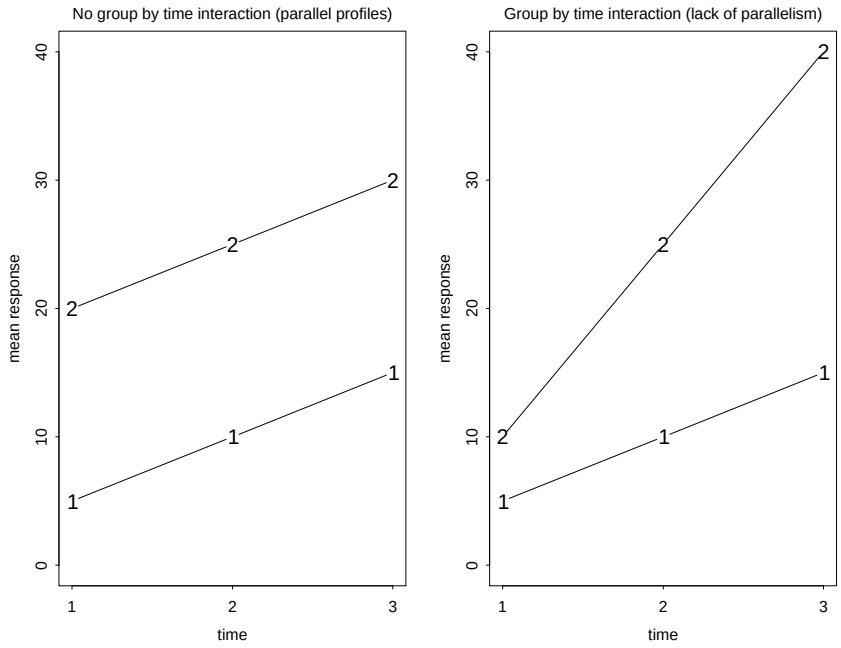
where $\boldsymbol{\mathcal{Y}}$ is the $(m \times n)$ matrix with ith row $\boldsymbol{Y}_i'$ and similarly for $\boldsymbol{\epsilon}$, and $\boldsymbol{A}$ is the $(m \times q)$ matrix with ith row $\boldsymbol{a}_i'$. We will not make direct use of this way of writing the model; we point it out as it is the way the model is often written in texts on general multivariate models. It is also the way the model is referred to in the documentation for `PROC GLM` in the SAS software package.

GROUP BY TIME INTERACTION: As we have noted, a common objective in the analysis of longitudinal data is to assess whether the way in which the response changes over time is different across treatment groups. This is usually phrased in terms of **means**. For example, in the dental study, is the **profile** of distance over time different **on average** for boys and girls? That is, is the pattern of change in mean response different for different groups?

This is best illustrated by picture. For the case of $q = 2$ groups and $n = 3$ time points, Figure 3 shows two possible scenarios. In each panel, the lines represent the mean responses $\mu_{\ell j}$ for each group. In both panels, the mean response at each time is higher for group 2 than for group 1 at all time points, and the pattern of change in mean response seems to follow a **straight line**. However, in the left panel, the **rate of change** of the mean response over time is **the same** for both groups.

I.e. the time **profiles** are **parallel**. In the right panel, the **rate of change** is faster for group 2; thus, the profiles are **not parallel**.

Figure 3: *Group by time interaction. Plotting symbol indicates group number.*



In the model, each point in the figure is represented by the form (5.13),

$$\mu_{\ell j} = \mu + \tau_\ell + \gamma_j + (\tau\gamma)_{\ell j}.$$

Here, the terms $(\tau\gamma)_{\ell j}$ represent the special amounts by which the mean for group ℓ at time j may differ from the overall mean. The difference in mean between groups 1 and 2 at any specific time j is, under the model,

$$\mu_{1j} - \mu_{2j} = (\tau_1 - \tau_2) + \{(\tau\gamma)_{1j} - (\tau\gamma)_{2j}\}.$$

Thus, the terms $(\tau\gamma)_{\ell j}$ allow for the possibility that the difference between groups **may be different** at different times, as in the right panel of Figure 3 – the amount $\{(\tau\gamma)_{1j} - (\tau\gamma)_{2j})\}$ is specific to the particular time j.

Now, if the $(\tau\gamma)_{\ell j}$ were all the **same**, the difference would reduce to

$$\mu_{1j} - \mu_{2j} = (\tau_1 - \tau_2),$$

as the second piece would be equal to zero. Here, the difference in mean response between groups is the same at **all time points** and equal to $(\tau_1 - \tau_2)$ (which does not depend on j). This is the situation of the left panel of Figure 3.

Under the constraints

$$\sum_{\ell=1}^{q}(\tau\gamma)_{\ell j} = 0 = \sum_{j=1}^{n}(\tau\gamma)_{\ell j} \text{ for all } \ell, j,$$

if $(\tau\gamma)_{\ell j}$ are all **the same** for all ℓ, j, then it must be that

$$(\tau\gamma)_{\ell j} = 0 \text{ for all } \ell, j.$$

Thus, if we wished to discern between a situation like that in the left panel, of **parallel** profiles, and that in the right panel (lack of parallelism), addressing the issue of a common rate of change over time, we could state the **null hypothesis** as

$$H_0: \text{ all } (\tau\gamma)_{\ell j} = 0.$$

There are qn total parameters $(\tau\gamma)_{\ell j}$; however, if the constraints above hold, then having $(q-1)(n-1)$ of the $(\tau\gamma)_{\ell j}$ equal to 0 automatically requires the remaining ones to be zero as well. Thus, the hypothesis is really one about the behavior of $(q-1)(n-1)$ parameters, hence there are $(q-1)(n-1)$ **degrees of freedom** associated with this hypothesis.

GENERAL FORM OF HYPOTHESES: It turns out that, with the model expressed in the form (5.12), it is possible to express H_0 and other hypotheses of scientific interest in a unified way. This unified expression is not necessary to appreciate the hypotheses of interest; however, it is used in many texts on the subject and in the documentation for `PROC GLM` in SAS, so we digress for a moment to describe it.

Specifically, noting that $\boldsymbol{M}$ is the matrix whose rows are the mean vectors for the different treatment groups, it is possible to write formal statistical hypotheses as **linear functions** of the elements of $\boldsymbol{M}$. Let

- $\boldsymbol{C}$ be a $(c \times q)$ matrix with $c \leq q$ of full rank.
- $\boldsymbol{U}$ be a $(n \times u)$ matrix with $u \leq n$ of full rank.

Then it turns out that the null hypothesis corresponding to questions of scientific interest may be written in the form

$$H_0 : \boldsymbol{CMU} = \boldsymbol{0}.$$

Depending on the choice of the matrices $\boldsymbol{C}$ and $\boldsymbol{U}$, the **linear function** $\boldsymbol{CMU}$ of the elements of $\boldsymbol{M}$ (the individual means for different groups at different time points) may be made to address these different questions.

We now exhibit this for H_0 for the group by time interaction. For definiteness, consider the situation where there are $q = 2$ groups and $n = 3$ time points. Consider

$$\boldsymbol{C} = \begin{pmatrix} 1 & -1 \end{pmatrix},$$

so that $c = 1 = q - 1$. Then note that

$$\begin{aligned} \boldsymbol{CM} &= \begin{pmatrix} 1 & -1 \end{pmatrix} \begin{pmatrix} \mu_{11} & \mu_{12} & \mu_{13} \\ \mu_{21} & \mu_{22} & \mu_{23} \end{pmatrix} = \begin{pmatrix} \mu_{11} - \mu_{21}, & \mu_{12} - \mu_{22}, & \mu_{13} - \mu_{23} \end{pmatrix} \\ &= \begin{pmatrix} \tau_1 - \tau_2 + (\tau\gamma)_{11} - (\tau\gamma)_{21}, & \tau_1 - \tau_2 + (\tau\gamma)_{12} - (\tau\gamma)_{22}, & \tau_1 - \tau_2 + (\tau\gamma)_{13} - (\tau\gamma)_{23} \end{pmatrix} \end{aligned}$$

Thus, this $\boldsymbol{C}$ matrix has the effect of **taking differences** among groups.

Now let

$$\boldsymbol{U} = \begin{pmatrix} 1 & 0 \\ -1 & 1 \\ 0 & -1 \end{pmatrix},$$

so that $u = 2 = n - 1$. It is straightforward (try it) to show that

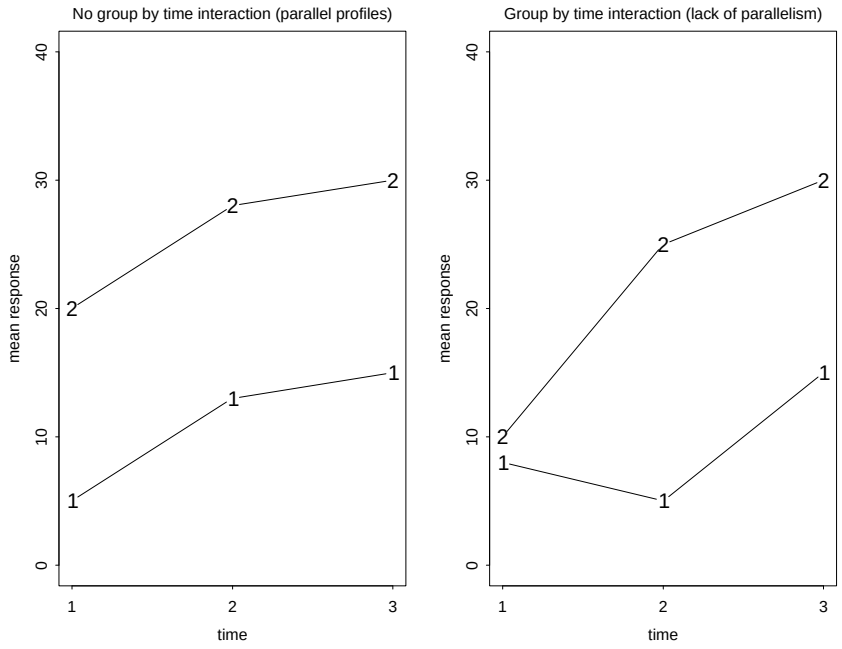
$$\begin{aligned} \boldsymbol{CMU} &= \begin{pmatrix} \mu_{11} - \mu_{21} - \mu_{12} + \mu_{22}, & \mu_{12} - \mu_{22} - \mu_{13} + \mu_{23} \end{pmatrix} \\ &= \begin{pmatrix} (\tau\gamma)_{11} - (\tau\gamma)_{21} - (\tau\gamma)_{12} + (\tau\gamma)_{22}, & (\tau\gamma)_{12} - (\tau\gamma)_{22} - (\tau\gamma)_{13} + (\tau\gamma)_{23} \end{pmatrix}. \end{aligned}$$

It is an exercise in algebra to verify that, under the constraints, if each of these elements equals zero, then H_0 follows.

In the jargon associated with repeated measurements, the test for group by time interaction is sometimes called the **test for parallelism**. Later, we will discuss some further hypotheses involving different choices of $\boldsymbol{U}$ that allow one to investigate different aspects of the change in mean response over time and how it differs across groups. Generally, in the analysis of longitudinal data from different groups, testing the group by time interaction is of primary interest, as it addresses whether the change in mean response differs across groups.

It is important to recognize that **parallelism** does not necessarily mean that the mean response over time is restricted to look like a **straight line** in each group. In Figure 4, the left panel exhibits parallelism; the right panel does not.

Figure 4: *Group by time interaction. Plotting symbol indicates group number.*



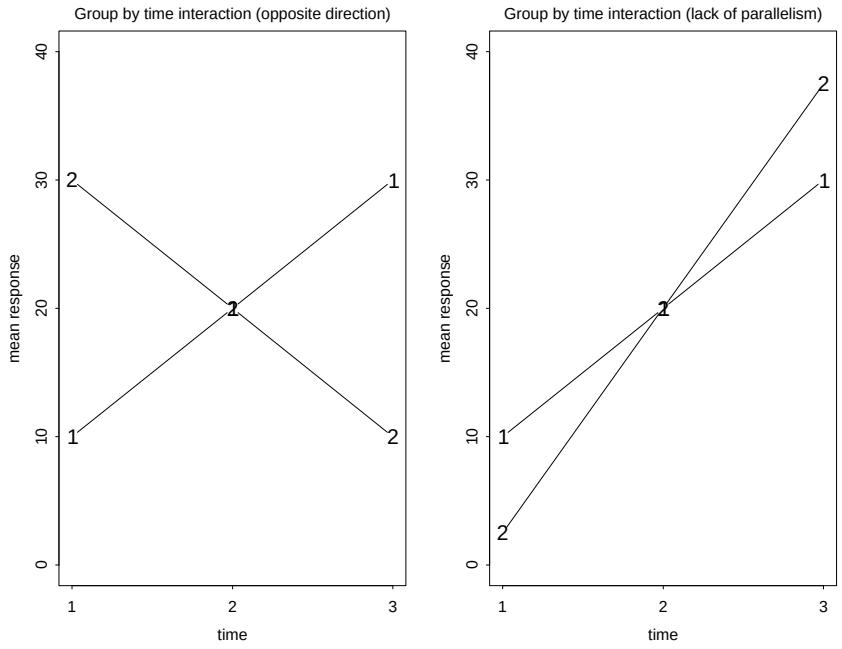
MAIN EFFECT OF GROUPS: Clearly, if profiles are parallel, then the obvious question is whether they are in fact **coincident**; that is, whether, at each time point, the mean response is in fact the same. A little thought shows that, if the profiles are parallel, then if the profiles are furthermore coincident, then the **average** of the mean responses over time will be the same for each group. Asking the question of whether the average of the mean responses over time is the same for each group if the profiles are **not parallel** may or may not be interesting or relevant.

- For example, if the true state of affairs were that depicted in the right panels of Figures 3 and 4 whether the average of mean responses over time is different for the two groups might be interesting, as it would be reflecting the fact that the mean response for group 2 is larger at all times.

- On the other hand, consider the left panel of Figure 5. If this were the true state of affairs, a test of this issue would be **meaningless**; the change of mean response over time is in the **opposite** direction for the two groups; thus, how it averages out over time is of little importance – because the phenomenon of interest does indeed happen **over time**, the **average** of what it does over time may be something that cannot be achieved – we can't make time stand still!

- Similarly, if the issue under study is something like growth, the **average** over time of the response may have little meaning; instead, one may be interested in, for example, how different the mean response is at the end of the time period of study. For example, in the right panel of Figure 5, the mean response over time increases for each group at different rates, but has the same average over time. Clearly, the group with the faster rate will have a larger mean response at the end of the time period.

Figure 5: *Group by time interaction. Plotting symbol indicates group number.*



Generally, then, whether the average of the mean response is the same across groups in a longitudinal study is of most interest in the case where the mean profiles over time are approximately parallel. For definiteness, consider the case of $q = 2$ groups and $n = 3$ time points.

We are interested in whether the average of mean responses over time is the same in each group. For group ℓ, this average is, with $n = 3$,

$$n^{-1}(\mu_{\ell 1} + \mu_{\ell 2} + \mu_{\ell 3}) = \mu + \tau_\ell + n^{-1}(\gamma_1 + \gamma_2 + \gamma_3) + n^{-1}\{(\tau\gamma)_{\ell 1} + (\tau\gamma)_{\ell 2} + (\tau\gamma)_{\ell 3}\}.$$

Taking the difference of the averages between $\ell = 1$ and $\ell = 2$, some algebra yields (verify)

$$\tau_1 - \tau_2 + n^{-1}\sum_{j=1}^{n}(\tau\gamma)_{1j} - n^{-1}\sum_{j=1}^{n}(\tau\gamma)_{2j}.$$

Note, however, that the **constraints** we impose so that the model is of **full rank** dictate that $\sum_{j=1}^{n}(\tau\gamma)_{\ell j} = 0$ for each ℓ; thus, the two sums in this expression are 0 by assumption, so that we are left with $\tau_1 - \tau_2$.

Thus, the hypothesis may be expressed as

$$H_0 : \tau_1 - \tau_2 = 0.$$

Furthermore, under the constraint $\sum_{\ell=1}^{q} \tau_\ell = 0$, if the τ_ℓ are equal as in H_0, then they must satisfy $\tau_\ell = 0$ for each ℓ. Thus, the hypothesis may be rewritten as

$$H_0 : \tau_1 = \tau_2 = 0.$$

For general q and n, the reasoning is the same; we have

$$H_0 : \tau_1 = \ldots = \tau_q = 0.$$

The appropriate null hypothesis that addresses this issue may also be stated in the general form $H_0 : \boldsymbol{CMU} = \boldsymbol{0}$ for suitable choices of $\boldsymbol{C}$ and $\boldsymbol{U}$. The form of $\boldsymbol{U}$ in particular shows the interpretation as that of "averaging" over time. Continuing to take $q = 2$ and $n = 3$, let

$$\boldsymbol{C} = \begin{pmatrix} 1 & -1 \end{pmatrix},$$

so that $c = 1 = q - 1$. Then note that

$$\begin{aligned} \boldsymbol{CM} &= \begin{pmatrix} 1 & -1 \end{pmatrix} \begin{pmatrix} \mu_{11} & \mu_{12} & \mu_{13} \\ \mu_{21} & \mu_{22} & \mu_{23} \end{pmatrix} = \begin{pmatrix} \mu_{11} - \mu_{21}, & \mu_{12} - \mu_{22}, & \mu_{13} - \mu_{23} \end{pmatrix} \\ &= \begin{pmatrix} \tau_1 - \tau_2 + (\tau\gamma)_{11} - (\tau\gamma)_{21}, & \tau_1 - \tau_2 + (\tau\gamma)_{12} - (\tau\gamma)_{22}, & \tau_1 - \tau_2 + (\tau\gamma)_{13} - (\tau\gamma)_{23} \end{pmatrix} \end{aligned}$$

Now let ($n = 3$ here)

$$\boldsymbol{U} = \begin{pmatrix} 1/n \\ 1/n \\ 1/n \end{pmatrix}.$$

It is straightforward to see that, with $n = 3$,

$$\boldsymbol{CMU} = \tau_1 - \tau_2 + n^{-1} \sum_{j=1}^{n} (\tau\gamma)_{1j} - n^{-1} \sum_{j=1}^{n} (\tau\gamma)_{2j}.$$

That is, this choice of $\boldsymbol{U}$ dictates an **averaging** operation across time. Imposing the constraints as above, we thus see that we may express H_0 in the form $H_0 : \boldsymbol{CMU} = 0$ with these choices of $\boldsymbol{C}$ and $\boldsymbol{U}$. For general q and n, one may specify appropriate choices of $\boldsymbol{C}$ and $\boldsymbol{U}$, where the latter is a column vector of 1's implying the "averaging" operation across time, and arrive at the general hypothesis $H_0 : \tau_1 = \ldots = \tau_q = 0$.

MAIN EFFECT OF TIME: Another question of interest may be whether the mean response is in fact **constant** over time. If the profiles are parallel, then this is like asking whether the mean response averaged across groups is the **same** at each time. If the profiles are not parallel, then this may or may not be interesting. For example, note that in the left panel of Figure 5, the average of mean responses for groups 1 and 2 are the same at each time point. However, the mean response is certainly not constant across time for either group. If the groups represent things like genders, then what happens on average is something that can never be achieved.

Consider again the special case of $q = 2$ and $n = 3$. The average of mean responses across groups for time j is

$$q^{-1}\sum_{\ell=1}^{q}\mu_{\ell j} = \gamma_j + q^{-1}\sum_{\ell=1}^{q}\tau_\ell + q^{-1}\sum_{\ell=1}^{q}(\tau\gamma)_{\ell j} = \gamma_j$$

using the constraints $\sum_{\ell=1}^{q}\tau_\ell = 0$ and $\sum_{\ell=1}^{q}(\tau\gamma)_{\ell j} = 0$. Thus, having all these averages be the same at each time is equivalent to

$$H_0 : \gamma_1 = \gamma_2 = \gamma_3.$$

Under the constraint $\sum_{j=1}^{n}\gamma_j = 0$, then, we have $H_0 : \gamma_1 = \gamma_2 = \gamma_3 = 0$.

For general q and n, the hypothesis is of the form

$$H_0 : \gamma_1 = \ldots = \gamma_n = 0.$$

We may also state this hypothesis in the form $H_0 : \boldsymbol{CMU} = \boldsymbol{0}$. In the special case $q = 2$, $n = 3$, taking

$$\boldsymbol{U} = \begin{pmatrix} 1 & 0 \\ -1 & 1 \\ 0 & -1 \end{pmatrix}, \quad \boldsymbol{C} = \begin{pmatrix} 1/2 & 1/2 \end{pmatrix}$$

gives

$$\begin{aligned} \boldsymbol{MU} &= \begin{pmatrix} \mu_{11} & \mu_{12} & \mu_{13} \\ \mu_{21} & \mu_{22} & \mu_{23} \end{pmatrix}\begin{pmatrix} 1 & 0 \\ -1 & 1 \\ 0 & -1 \end{pmatrix} = \begin{pmatrix} \mu_{11}-\mu_{12} & \mu_{12}-\mu_{13} \\ \mu_{21}-\mu_{22} & \mu_{22}-\mu_{23} \end{pmatrix} \\ &= \begin{pmatrix} \gamma_1-\gamma_2+(\tau\gamma)_{11}-(\tau\gamma)_{12}, & \gamma_2-\gamma_3+(\tau\gamma)_{12}-(\tau\gamma)_{13} \\ \gamma_1-\gamma_2+(\tau\gamma)_{21}-(\tau\gamma)_{22}, & \gamma_2-\gamma_3+(\tau\gamma)_{22}-(\tau\gamma)_{23} \end{pmatrix}. \end{aligned}$$

from whence it is straightforward to derive, imposing the constraints, that (verify)

$$\boldsymbol{CMU} = \begin{pmatrix} \gamma_1-\gamma_2, & \gamma_2-\gamma_3 \end{pmatrix}.$$

Setting this equal to zero gives $H_0 : \gamma_1 = \gamma_2 = \gamma_3$. For general q and n, we may choose the matrices $\boldsymbol{C}$ and $\boldsymbol{U}$ in a similar fashion. Note that this type of $\boldsymbol{C}$ matrix **averages** across groups.

OBSERVATION: These are, of course, exactly the hypotheses that one tests for a split plot experiment, where, here, "time" plays the role of the "split plot" factor and "group" is the "whole plot factor." What is different lies in the interpretation; because "time" has a natural **ordering** (longitudinal), what is interesting may be different; as noted above, of primary interest is whether the change in mean response is different over (the levels of) time. We will see more on this shortly.

5.4 Analysis of variance

Given the fact that the statistical model and hypotheses in this setup are identical to that of a split plot experiment, it should come as no surprise that the analysis performed is identical. That is, under the assumption that the model (5.1) is correct and that the observations are normally distributed, it is possible to show that the usual F ratios one would construct under the usual principles of analysis of variance provide the basis for valid tests of the hypotheses above. We write out the analysis of variance table here using the original notation with three subscripts, i.e., $Y_{h\ell j}$ represents the measurement at the j time on the hth unit in the ℓth group.

Define

- $\overline{Y}_{h\ell\cdot} = n^{-1}\sum_{j=1}^{n} Y_{h\ell j}$, the sample average over time for the hth unit in the ℓth group (over all observations on this unit)
- $\overline{Y}_{\cdot\ell j} = r_\ell^{-1}\sum_{h=1}^{r_\ell} Y_{h\ell j}$, the sample average at time j in group ℓ over all units
- $\overline{Y}_{\cdot\ell\cdot} = (r_\ell n)^{-1}\sum_{h=1}^{r_\ell}\sum_{j=1}^{n} Y_{h\ell j}$, the sample average of all observations in group ℓ
- $\overline{Y}_{\cdot\cdot j} = m^{-1}\sum_{\ell=1}^{q}\sum_{h=1}^{r_\ell} Y_{h\ell j}$, the sample average of all observations at the jth time
- $\overline{Y}_{\cdots}$ = the average of all mn observations.

Let

$$SS_G = \sum_{\ell=1}^{q} n r_\ell (\overline{Y}_{\cdot\ell\cdot} - \overline{Y}_{\cdots})^2, \quad SS_{Tot,U} = n\sum_{\ell=1}^{q}\sum_{h=1}^{r_\ell}(\overline{Y}_{h\ell\cdot} - \overline{Y}_{\cdots})^2$$

$$SS_T = m\sum_{j=1}^{n}(\overline{Y}_{\cdot\cdot j} - \overline{Y}_{\cdots})^2, \quad SS_{GT} = \sum_{j=1}^{n}\sum_{\ell=1}^{q} r_\ell(\overline{Y}_{\cdot\ell j} - \overline{Y}_{\cdots})^2 - SS_T - SS_G$$

$$SS_{Tot,all} = \sum_{\ell=1}^{q}\sum_{h=1}^{r_\ell}\sum_{j=1}^{n}(Y_{h\ell j} - \overline{Y}_{\cdots})^2.$$

Then the following analysis of variance table is usually constructed.

Source	SS	DF	MS	F
Among Groups	SS_G	$q-1$	MS_G	$F_G = MS_G/MS_{EU}$
Among-unit Error	$SS_{Tot,U} - SS_G$	$m-q$	MS_{EU}	
Time	SS_T	$n-1$	MS_T	$F_T = MS_T/MS_E$
Group $\times$ Time	SS_{GT}	$(q-1)(n-1)$	MS_{GT}	$F_{GT} = MS_{GT}/MS_E$
Within-unit Error	SS_E	$(m-q)(n-1)$	MS_E	
Total	$SS_{Tot,all}$	$nm-1$		

where $SS_E = SS_{Tot,all} - SS_{GT} - SS_T - SS_{Tot,U}$.

"ERROR": Keep in mind that, although it is traditional to use the term "error" in analysis of variance, the **among-unit error** term includes variation due to **among-unit biological variation** and the **within-unit error** term includes variation due to both fluctuations and measurement error.

F-RATIOS: It may be shown that, **as long as** the model is correct and the observations are normally distributed, the F ratios in the above table do indeed have sampling distributions that are F distributions under the null hypotheses discussed above. It is instructive to state this another way. If we think of the data in terms of **vectors**, then this is equivalent to saying that we require that

$$\boldsymbol{Y}_i \sim \mathcal{N}_n(\boldsymbol{\mu}_i, \boldsymbol{\Sigma}), \quad \boldsymbol{\Sigma} = \sigma_b^2 \boldsymbol{J}_n + \sigma_e^2 \boldsymbol{I}_n. \tag{5.15}$$

That is, as long as the data vectors are multivariate normal and exhibit the **compound symmetry** covariance structure, then the F ratios above, which may be seen to be based on calculations on individual observations, do indeed have sampling distributions that are F with the obvious degrees of freedom.

EXPECTED MEAN SQUARES: In fact, under (5.15), it is possible to derive the **expectations** of the mean squares in the table. That is, we find the average over all data sets we might have ended up with, of the MSs that are used to construct the F ratios by applying the expectation operator to each expression (which is a function of the data).

The calculations are messy (one place where they are done is in section 3.3 of Crowder and Hand, 1990), so we do not show them here. The following summarizes the expected mean squares under (5.15).

Source	MS	Expected mean square
Among Groups	MS_G	$\sigma_e^2 + n\sigma_b^2 + n\sum_{\ell=1}^{q} r_\ell \tau_\ell^2/(q-1)$
Among-unit error	MS_{EU}	$\sigma_e^2 + n\sigma_b^2$
Time	MS_T	$\sigma_e^2 + m\sum_{j=1}^{n} \gamma_j^2/(n-1)$
Group $\times$ Time	MS_{GT}	$\sigma_e^2 + \sum_{\ell=1}^{q} r_\ell \sum_{j=1}^{n} (\tau\gamma)_{\ell j}^2/(q-1)(n-1)$
Within-unit Error	MS_E	σ_e^2

It is **critical** to recognize that these calculations are only valid if the model is **correct**, i.e. if (5.15) holds.

Inspection of the expected mean squares shows informally that we expect the F ratios in the analysis of variance table to test the appropriate issues. For example, we would expect F_{GT} to be large if the $(\tau\gamma)_{\ell j}$ were not all zero. Note that F_G uses the appropriate denominator; intuitively, because we base our assessment on averages of across all units **and** time points, we would wish to compare the mean square for groups against an "error term" that takes into account **all** sources of variation among observations we have on the units – both that attributable to the fact that units vary in the population (σ_b^2) and that attributable to the fact that individual observations vary within units (σ_e^2). The other two tests are on features that occur **within units**; thus, the denominator takes account of the relevant source of variation, that within units (σ_e^2).

We thus have the following test procedures.

- **Test of the Group by Time interaction (parallelism)**.

  $$H_0 : (\tau\gamma)_{\ell j} = 0 \text{ for all } j, \ell \text{ vs. } H_1 : \text{ at least one } (\tau\gamma)_{\ell j} \neq 0.$$

  A valid test rejects H_0 at level of significance α if

  $$F_{GT} > \mathcal{F}_{(q-1)(n-1),(n-1)(m-q),\alpha}$$

  or, equivalently, if the probability is less than α that one would see a value of the test statistic as large or larger than F_{GT} if H_0 were true (that is, the p-value is less than α).

- **Test of Main effect of Time (constancy)**.

  $$H_0 : \gamma_j = 0 \text{ for all } j \text{ vs. } H_1 : \text{ at least one } \gamma_j \neq 0.$$

  A valid test rejects H_0 at level α if

  $$F_T > \mathcal{F}_{n-1,(n-1)(m-q),\alpha}$$

  or, equivalently, if the probability is less than α that one would see a value of the test statistic as large or larger than F_T if H_0 were true.

- **Test of Main effect of Group (coincidence)**.

  $$H_0 : \tau_\ell = 0 \text{ for all } \ell \text{ vs. } H_1 : \text{ at least one } \tau_\ell \neq 0.$$

  A valid test rejects H_0 at level of significance α if

  $$F_G > \mathcal{F}_{q-1,m-q,\alpha}$$

  or, equivalently, if the probability is less than α that one would see a value of the test statistic as large or larger than F_G if H_0 were true.

In the above, $\mathcal{F}_{a,b,\alpha}$ critical value corresponding to α for an F distribution with a numerator and b denominator degrees of freedom.

In section 5.8, we show how one may use SAS `PROC GLM` to perform these calculations.

5.5 Violation of covariance matrix assumption

In the previous section, we emphasized that the procedures based on the analysis of variance are only valid if the assumption of **compound symmetry** holds for the covariance matrix of a data vector. In reality, these procedures are still valid under slightly more general conditions. **However**, the important issue remains that the covariance matrix must be of a special form; if it is not, the tests above will be invalid and may lead to erroneous conclusions. That is, the F ratios F_T and F_{GT} will no longer have exactly an F distribution.

A $(n \times n)$ matrix $\boldsymbol{\Sigma}$ is said to be of **Type H** if it may be written in the form

$$\boldsymbol{\Sigma} = \begin{pmatrix} \lambda + 2\alpha_1 & \alpha_1 + \alpha_2 & \cdots & \alpha_1 + \alpha_n \\ \alpha_2 + \alpha_1 & \lambda + 2\alpha_2 & \cdots & \alpha_2 + \alpha_n \\ \vdots & \vdots & \vdots & \vdots \\ \alpha_n + \alpha_1 & \alpha_n + \alpha_2 & \cdots & \lambda + 2\alpha_n \end{pmatrix}. \tag{5.16}$$

It is straightforward (convince yourself) that a matrix that exhibits **compound symmetry** is of Type H.

It is possible to show, although we will not pursue this here, that, as long as the data vectors $\boldsymbol{Y}_i$ are multivariate normal with common covariance matrix $\boldsymbol{\Sigma}$ that is of the form (5.16), the F tests discussed above will be valid. Thus, because (5.16) includes the **compound symmetry** assumption as a special case, these F tests will be valid if model (5.1) holds (along with normality).

- If the covariance matrix $\boldsymbol{\Sigma}$ is **not** of Type H, but these F tests are conducted nonetheless, they will be too **liberal**; that is, they will tend to reject the null hypothesis more often then they should.
- Thus, one possible consequence of using the analysis of variance procedures when they are not appropriate is to conclude that group by time interactions exist when they really don't.

TEST OF SPHERICITY: It is thus of interest to be able to test whether the true covariance structure of data vectors in a repeated measurement context is indeed of Type H. One such test is known as Mauchly's test for sphericity. The form and derivation of this test are beyond the scope of our discussion here; a description of the test is given by Vonesh and Chinchilli (1997, p. 85), for example. This test provides a test statistic for testing the null hypothesis

$$H_0 : \boldsymbol{\Sigma} \text{ is of Type H},$$

where $\boldsymbol{\Sigma}$ is the true covariance matrix of a data vector.

The test statistic, which we do not give here, has approximately a χ^2 (chi-square) distribution when the number of units m on test is "large" with degrees of freedom equal to $(n-2)(n+1)/2$. Thus, the test is performed at level of significance α by comparing the value of the test statistic to the χ^2_α critical value with $(n-2)(n+1)/2$ degrees of freedom. SAS `PROC GLM` may be instructed to compute this test when repeated measurement data are being analyzed; this is shown in section 5.8.

The test has some limitations:

- It is not very powerful when the numbers of units in each group is not large
- It can be misleading if the data vectors really do not have a multivariate normal distribution.

These limitations are one of the reasons we do not discuss the test in more detail; it may be of limited practical value.

In section 5.7, we will discuss one approach to handling the problem of what to do if the null hypothesis is rejected or if one is otherwise dubious about the assumption of Type H covariance.

5.6 Specialized within-unit hypotheses and tests

The hypotheses of group by time interaction (parallelism) and main effect of time have to do with questions about what happens over time; as time is a **within-unit** factor, these tests are often referred to as focusing on within-unit issues. These hypotheses address these issues in an "overall" sense; for example, the group by time interaction hypothesis asks whether the pattern of mean response over time is different for different groups.

Often, it is of interest to carry out a more **detailed** study of specific aspects of how the mean response behaves over time, as we now describe. We first review the following definition.

CONTRASTS: Formally, if $\boldsymbol{c}$ is a $(n \times 1)$ vector and $\boldsymbol{\mu}$ is a $(n \times 1)$ vector of means, then the **linear combination**

$$\boldsymbol{c}'\boldsymbol{\mu} = \boldsymbol{\mu}'\boldsymbol{c}$$

is called a **contrast** if $\boldsymbol{c}$ is such that its elements sum to zero.

Contrasts are of interest in the sense that hypotheses about differences of means can be expressed in terms of them. In particular, if $\boldsymbol{c}'\boldsymbol{\mu} = 0$, there is no difference.

For example, consider $q = 2$ and $n = 3$. The **contrasts**

$$\mu_{11} - \mu_{12} \quad \text{and} \quad \mu_{21} - \mu_{22} \tag{5.17}$$

compare the mean response at the first and second time points for each of the 2 groups; similarly, the contrasts

$$\mu_{12} - \mu_{13} \quad \text{and} \quad \mu_{22} - \mu_{23} \tag{5.18}$$

compare the mean response at the second and third time points for each group. Thus, these contrasts address the issue of how the mean differs from one time to the next in each group.

Recalling

$$\boldsymbol{\mu}_1' = \begin{pmatrix} \mu_{11} & \mu_{12} & \mu_{13} \end{pmatrix}, \quad \boldsymbol{\mu}_2' = \begin{pmatrix} \mu_{21} & \mu_{22} & \mu_{23} \end{pmatrix},$$

we see that the contrasts in (5.17) result from postmultiplying these mean vectors for each group by

$$\boldsymbol{c} = \begin{pmatrix} 1 \\ -1 \\ 0 \end{pmatrix};$$

similarly, those in (5.18) result from postmultiplying by

$$\boldsymbol{c} = \begin{pmatrix} 0 \\ 1 \\ -1 \end{pmatrix}.$$

Specialized questions of interest pertaining to how the mean differs from one time to the next may then be stated.

- We may be interested in whether the way in which the mean differs from, say, time 1 to time 2 is **different** for different groups. This is clearly **part of** the overall group by time interaction, focusing particularly on what happens between times 1 and 2.

  For our two groups, we would thus be interested in the **difference** of the contrasts in (5.17).

  We may equally well wish to know whether the way in which the mean differs from time 2 to time 3 is different across groups; this is of course also a part of the group by time interaction, and is represented formally by the difference of the contrasts in (5.18).

- We may be interested in whether there is a difference in mean from, say, time 1 to time 2, **averaged across groups**. This is clearly **part** of the main effect of time and would be formally represented by **averaging** the contrasts in (5.17). For times 2 and 3, we would be interested in the average of the contrasts in (5.18).

Specifying these specific contrasts and then considering their differences among groups or averages across groups is a way of "picking apart" how the overall group by time effect and main effect of time occur and can thus provide additional insight on how and whether things change over time.

It turns out that we may express such contrasts succinctly through the representation $\boldsymbol{CMU}$; indeed, this is the way in which such specialized hypotheses are presented documentation for `PROC GLM` in SAS.

To obtain the contrasts in (5.17) and (5.18), in the case $q = 2$ and $n = 3$, consider the $n \times (n-1)$ matrix

$$\boldsymbol{U} = \begin{pmatrix} 1 & 0 \\ -1 & 1 \\ 0 & -1 \end{pmatrix}.$$

Then note that

$$\boldsymbol{MU} = \begin{pmatrix} \mu_{11} & \mu_{12} & \mu_{13} \\ \mu_{21} & \mu_{22} & \mu_{23} \end{pmatrix} \begin{pmatrix} 1 & 0 \\ -1 & 1 \\ 0 & -1 \end{pmatrix} = \begin{pmatrix} \mu_{11} - \mu_{12} & \mu_{12} - \mu_{13} \\ \mu_{21} - \mu_{22} & \mu_{22} - \mu_{23} \end{pmatrix}. \tag{5.19}$$

Each element of the resulting matrix is one of the above contrasts. This choice of the **contrast matrix** $\boldsymbol{U}$ thus summarizes contrasts that have to do with differences in means from one time to the next. Each column represents a different possible contrast of this type.

Note that the same matrix $\boldsymbol{U}$ would be applicable for larger q – the important point is that it has $n-1$ columns, each of which applies one of the $n-1$ possible comparisons of a mean at a particular time to that subsequent. For general n, the matrix would have the form

$$\boldsymbol{U} = \begin{pmatrix} 1 & 0 & \cdots & 0 \\ -1 & 1 & \cdots & 0 \\ 0 & -1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots \\ 0 & \cdots & \cdots & 1 \\ 0 & \cdots & 0 & -1 \end{pmatrix} \tag{5.20}$$

with n and $n-1$ columns. Postmultiplication of $\boldsymbol{M}$ by the general form of contrast matrix $\boldsymbol{U}$ in (5.20) is often called the **profile transformation** of within-unit means.

Other contrasts may be of interest. Instead of asking what happens from one time to the next, we may focus on how the mean at each time differs from what happens over all subsequent times. This may help us to understand at what point in time things seem to change (if they do).

For example, taking $q = 2$ and $n = 4$, consider the contrast

$$\mu_{11} - (\mu_{12} + \mu_{13} + \mu_{14})/3.$$

This contrast compares, for group 1, the mean at time 1 to the **average** of the means at all other times. Similarly

$$\mu_{12} - (\mu_{13} + \mu_{14})/2$$

compares for group 1 the mean at time 2 to the average of those at subsequent times. The final contrast of this type for group 1 is

$$\mu_{13} - \mu_{14},$$

which compares what happens at time 3 to the "average" of what comes next, which is the single mean at time 4.

We may similarly specify such contrasts for the other group.

We may express all such contrasts by a different contrast matrix $\boldsymbol{U}$. In particular, let

$$\boldsymbol{U} = \begin{pmatrix} 1 & 0 & 0 \\ -1/3 & 1 & 0 \\ -1/3 & -1/2 & 1 \\ -1/3 & -1/2 & -1 \end{pmatrix}, \tag{5.21}$$

Then if $q = 2$ (verify),

$$\boldsymbol{MU} = \begin{pmatrix} \mu_{11} - \mu_{12}/3 - \mu_{13}/3 - \mu_{14}/3, & \mu_{12} - \mu_{13}/2 - \mu_{14}/2, & \mu_{13} - \mu_{14} \\ \mu_{21} - \mu_{22}/3 - \mu_{23}/3 - \mu_{24}/3, & \mu_{22} - \mu_{23}/2 - \mu_{24}/2, & \mu_{23} - \mu_{24} \end{pmatrix},$$

which expresses all such contrasts; the first row gives the ones for group 1 listed above.

For general n, the $(n \times n-1)$ matrix whose columns define contrasts of this type is the so-called **Helmert transformation** matrix of the form

$$\boldsymbol{U} = \begin{pmatrix} 1 & 0 & 0 & \cdots & 0 \\ -1/(n-1) & 1 & 0 & \cdots & 0 \\ -1/(n-1) & -1/(n-2) & 1 & \cdots & 0 \\ \vdots & \vdots & -1/(n-3) & \vdots & \vdots \\ -1/(n-1) & -1/(n-2) & \vdots & \cdots & 1 \\ -1/(n-1) & -1/(n-2) & -1/(n-3) & \cdots & -1 \end{pmatrix}, \tag{5.22}$$

Postmultiplication of $\boldsymbol{M}$ by a matrix of the form (5.22) in contrasts representing comparisons of each mean against the **average** of means at all subsequent times.

It is straightforward to verify (try it!) that with $n = 3$ and $q = 2$, this transformation would lead to

$$\boldsymbol{MU} = \begin{pmatrix} \mu_{11} - \mu_{12}/2 - \mu_{13}/2 & \mu_{12} - \mu_{13} \\ \mu_{21} - \mu_{22}/2 - \mu_{23}/2 & \mu_{22} - \mu_{23} \end{pmatrix} \tag{5.23}$$

How do we use all of this?

OVERALL TESTS: We have already seen the use of the $\boldsymbol{CMU}$ representation for the overall tests of group by time interaction and main effect of time. Both contrast matrices $\boldsymbol{U}$ in (5.19) (profile) and (5.23) (Helmert) contain sets of $n-1$ contrasts that "pick apart" all possible differences in means over time in different ways. Thus, intuitively we would expect that either one of them would lead us to the overall tests for group by time interaction and main effect of time given the right $\boldsymbol{C}$ matrix (one that takes differences over groups or one that averages over groups, respectively).

This is indeed the case: It may be shown that premultiplication of **either** (5.19) or (5.23) by the same matrix $\boldsymbol{C}$ will lead to the **same** overall hypotheses in terms of the model components γ_j and $(\tau\gamma)_{\ell j}$. For example, we already saw that premultiplying (5.19) by $\boldsymbol{C} = (1, 1)$ gives with the constraints on $(\tau\gamma)_{\ell j}$

$$\boldsymbol{CMU} = \begin{pmatrix} \gamma_1 - \gamma_2, & \gamma_2 - \gamma_3 \end{pmatrix} = \mathbf{0}.$$

It may be shown that premultiplying (5.23) by the same matrix $\boldsymbol{C}$ yields (try it)

$$\boldsymbol{CMU} = \begin{pmatrix} \gamma_1 - 0.5\gamma_2 - 0.5\gamma_3, & \gamma_2 - \gamma_3 \end{pmatrix} = \mathbf{0}.$$

It is straightforward to verify that, these both imply the same thing, namely, that we are testing $\gamma_1 = \gamma_2 = \gamma_3$.

OVERALL TESTS: This shows the general phenomenon that the choice of the matrix of contrasts $\boldsymbol{U}$ is not important for dictating the general tests of Time main effects and Group by Time interaction. As long as the matrix is such that it yields differences of mean responses at different times, it will give the same form of the overall hypotheses.

The choice of $\boldsymbol{U}$ matrix **is** important when we are interested in "picking apart" these overall effects, as above.

We now return to how we might represent hypotheses for and conduct tests of issues like those laid out on page 135. for a given contrast matrix $\boldsymbol{U}$ of interest. Premultiplication of $\boldsymbol{U}$ by $\boldsymbol{M}$ will yield the $q \times (n-1)$ matrix $\boldsymbol{MU}$ whose ℓth row contains whatever contrasts are of interest (dictated by the columns of $\boldsymbol{U}$) for group ℓ.

- If we premultiply $\boldsymbol{MU}$ by the $(q-1) \times q$ matrix

$$\boldsymbol{C} = \begin{pmatrix} 1 & -1 & 0 & \cdots & 0 \\ 1 & 0 & -1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 1 & 0 & 0 & \cdots & -1 \end{pmatrix}$$

  (we considered earlier the special case where $q = 2$), then for each contrast defined in $\boldsymbol{U}$, the result is to consider how that contrast differs across groups. The contrast considers a specific part of the way that mean response differs among the times, so is a component of the Group by Time interaction (how the difference in mean across groups is different at different times.)

- If we premultiply by $\boldsymbol{C} = (1/q, 1/q, \ldots, 1/q)$, each of the $n-1$ elements of the resulting $1 \times (n-1)$ matrix correspond to the **average** of each of these contrasts over groups, which all together constitute the Time main effect. If we consider one of these elements on its own, we see that it represents the contrast of mean response at time j to average mean response at all times after j, **averaged** across groups. If that contrast were equal to zero, it would say that, averaged across groups, the mean response at time j, is equal to the average of subsequent mean responses.

As we noted earlier, we may wish to look at each of these **separately** to explore particular aspects of how the mean response over time behaves. That is, we may wish to consider **separate** hypothesis tests addressing these issues.

SEPARATE TESTS: Carrying out separate hypothesis tests for each contrast in $\boldsymbol{U}$ may be accomplished operationally as follows. Consider the kth column of $\boldsymbol{U}$, $\boldsymbol{c}_k$, $k = 1, \ldots, n-1$.

- Apply the function dictated by that column of $\boldsymbol{U}$ to each unit's data vector. That is, for each vector $\boldsymbol{Y}_{h\ell}$, the operation implied is

$$\boldsymbol{y}'_{h\ell}\boldsymbol{c}_k = \boldsymbol{c}'_k\boldsymbol{Y}_{h\ell}.$$

  This distills down the repeated measurements on each unit to a **single number** representing the value of the contrast for that unit. If each unit's data vector has the same covariance matrix $\boldsymbol{\Sigma}$, then each of these "distilled" data values has the **same variance** across all units (see below).

- Perform analyses on the resulting "data;" e.g. to test whether the contrast differs across groups, one may conduct a usual one-way analysis of variance on these "data."

- To test whether the contrast is zero averaged across groups, test whether the overall mean of the "data" is equal to zero using using a standard t test (or equivalently, the F test based on the square of the t statistic).

- These tests will be valid **regardless** of whether **compound symmetry** holds; all that matters is that $\boldsymbol{\Sigma}$, whatever it is, is **the same** for all units. The variance of a distilled data value $\boldsymbol{c}_k'\boldsymbol{Y}_{h\ell}$ for the hth unit in group ℓ is

$$\text{var}\, \boldsymbol{c}_k'\boldsymbol{Y}_{h\ell} = \boldsymbol{c}_k'\boldsymbol{\Sigma}\boldsymbol{c}_k.$$

  This is a constant for all h and ℓ as long as $\boldsymbol{\Sigma}$ is the same. Thus, the usual assumption of constant variance that is necessary for a one-way analysis of variance is fulfilled for the "data" corresponding to each contrast.

ORTHOGONAL CONTRASTS: In some instances, note that the contrasts making up one of these transformation matrices have an additional property. Specifically, if $\boldsymbol{c}_1$ and $\boldsymbol{c}_2$ are any two columns for the matrix, then if

$$\boldsymbol{c}_1'\boldsymbol{c}_2 = 0;$$

i.e. the sum of the product of corresponding elements of the two columns is zero, the **vectors** $\boldsymbol{c}_1$ and $\boldsymbol{c}_2$ are said to be **orthogonal**. The **contrasts** corresponding to these vectors are said to be **orthogonal contrasts**.

- The contrasts making up the profile transformation are **not** orthogonal (verify).
- The contrasts making up the Helmert transformation **are** orthogonal (verify).

The advantage of having a transformation whose contrasts are orthogonal is as follows.

NORMALIZED ORTHOGONAL CONTRASTS: For a set of **orthogonal contrasts**, the separate tests for each have a nice property not possessed by sets of nonorthogonal contrasts. As intuition might suggest, if contrasts are indeed **orthogonal**, they ought to **partition** the total Group by Time interaction and Within-Unit Error sums of squares into $n-1$ distinct or "nonoverlapping" components. This means that the outcome of one of the tests may be viewed without regard to the outcome of the others.

It turns out that if one works with a properly "**normalized**" version of a $\boldsymbol{U}$ matrix whose columns are orthogonal, then this property can be seen very clearly. In particular, the sums of squares for group in each separate ANOVA for each contrasts **add up** to the sum of squares SS_{GT}! Similarly, the error sums of squares add up to SS_E.

To appreciate this, consider the Helmert matrix in (5.21),

$$\boldsymbol{U} = \begin{pmatrix} 1 & 0 & 0 \\ -1/3 & 1 & 0 \\ -1/3 & -1/2 & 1 \\ -1/3 & -1/2 & -1 \end{pmatrix}.$$

Each column corresponds to a different **function** to be applied to the data vectors for each unit, i.e. the kth column describes the kth contrast function $\boldsymbol{c}_k'\boldsymbol{Y}_{h\ell}$ of a data vector. Now the constants that make up each $\boldsymbol{c}_k$ are different for each k; thus, the values of $\boldsymbol{c}_k'\boldsymbol{Y}_{h\ell}$ for each k are on **different scales** of measurement. They are not comparable across all $n-1$ contrasts, and thus the sums of squares from each individual ANOVA are not comparable, because they each work with "data" on different scales.

It is possible to modify each contrast without affecting the orthogonality condition or the issue addressed by each contrast so that the resulting "data" **are** scaled similarly. Note that the sums of the **squared** elements of each column are different, i.e. the sums of squares of the first, second, and third columns are

$$1^2 + (-1/3)^2 + (-1/3)^2 + (-1/3)^2 = 4/3,$$

3/2 and 2, respectively. This illustrates that the contrasts are indeed not scaled similarly and suggests the modification.

- Multiply each contrast by an appropriate constant so that the sums of the squared elements is equal to 1.
- In our example, note that if we multiply the first column by $\sqrt{3/4}$, the second by $\sqrt{2/3}$, and the third by $\sqrt{1/2}$, then it may be verified that the sum of squares of the modified elements is equal to 1 in each case; e.g. $\{\sqrt{3/4}(1)\}^2 + \{\sqrt{3/4}(-1/3)\}^2 + \{\sqrt{3/4}(-1/3)\}^2 + \{\sqrt{3/4}(-1/3)\}^2 = 1$.
- Note that multiplying each contrast by a constant does not change the spirit of the hypothesis tests to which it corresponds; e.g. for the first column, testing

  $$H_0 : \mu_{11} - \mu_{12}/3 - \mu_{13}/3 - \mu_{14}/3 = 0$$

  is the same as testing $H_0 : \sqrt{3/4}\mu_{11} - \sqrt{3/4}\mu_{12}/3 - \sqrt{3/4}\mu_{13}/3 - \sqrt{3/4}\mu_{14}/3 = 0$. When all contrasts in an orthogonal transformation are scaled similarly in this way, then they are said to be **orthonormal.**

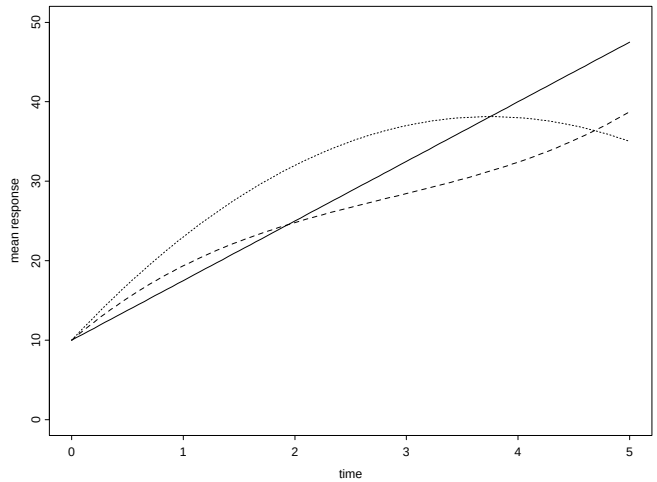
- The resulting "data" corresponding to the modified versions of the contrasts **will** be on the same scale. It then is the case that the sums of squares for each individual ANOVA do indeed add up.

Although this is a pleasing property, it is not necessary to use the normalized version of contrasts to obtain the correct test statistics for each contrast. Even if a set of $n-1$ orthogonal contrasts is not normalized in this way, the **same** test statistics will result. Although each separate ANOVA is on a different scale so that the sums of squares for group and error in each will not add up to SS_{GT} and SS_E, the F ratios formed **will** be the same, because the scaling factor will "cancel out" from the numerator and denominator of the F ratio and give the same statistic. The orthonormal version of the transformation is often thought of simply because it leads to the nice, additive property.

If contrasts are not orthogonal, the interpretation of the separate tests is more difficult because the separate tests no longer are "nonoverlapping." The overall sum of squares for Group by Time is no longer partitioned as above. Thus, how one test comes out is related to how another one comes out.

ORTHOGONAL POLYNOMIAL CONTRASTS: As we saw in the examples in Chapter 1, a common feature of longitudinal data is that each unit appears to exhibit a "smooth" time **trajectory**. In some cases, like the dental study, this appears to be a straight line. In other cases, like the soybean growth study (Example 3), the trajectories seem to "curve." Thus, if we were to consider the trajectory of a single unit, it might be reasonable to think of it as a linear, quadratic, cubic, in general, a **polynomial** function of time. (Later in the course, we will be much more explicit about this view.) Figure 6 shows such trajectories.

Figure 6: *Polynomial trajectories: linear (solid), quadratic (dots), cubic (dashes)*



In this situation, it would be advantageous to be able to consider behavior of the mean response over time (averaged across and among groups) in a way that acknowledges this kind of pattern. For example, in the dental study, we might like to ask

- Averaged across genders, is there a **linear** (straight line) trend over time? Is there a **quadratic** trend?
- Does this **linear** or **quadratic** trend differ across genders?

There is a particular type of contrast that focuses on this issue, whose coefficients are referred to as **orthogonal polynomial coefficients**.

If we have data at n time points on each unit, then, in principle, it would be possible to fit up to a $(n-1)$ degree polynomial in time. Thus, for such a situation, it is possible to define $n-1$ **orthogonal polynomial contrasts**, each measuring the strength of the linear, quadratic, cubic, and so on contribution to the $n-1$ degree polynomial. This is possible both for time points that are **equally spaced** over time and **unequally spaced**. The details of how these contrasts are defined are beyond our scope here. For equally-spaced times, the coefficients of the $n-1$ orthogonal polynomials are available in tables in many statistics texts (e.g. Steel, Torrie, and Dickey, 1997, p. 390); for unequally-spaced times points, the computations depend on the time points themselves.

Statistical software such as SAS `PROC GLM` offers computation of orthogonal polynomial contrasts, so that the user may focus on interpretation rather than nasty computation. As an example, the following $\boldsymbol{U}$ matrix has columns corresponding to the $n-1$ orthogonal polynomial contrasts (in the order linear, quadratic, cubic) in the case $n = 4$:

$$\boldsymbol{U} = \begin{pmatrix} -3 & 1 & -1 \\ -1 & -1 & 3 \\ 1 & -1 & -3 \\ 3 & 1 & 1 \end{pmatrix}.$$

With the appropriate set of orthogonal polynomial contrasts, one may proceed as above to conduct hypothesis tests addressing the strength of the linear, quadratic, and so on components of the profile over time. The orthogonal polynomial transformation may also be "normalized" as discussed above.

5.7 Adjusted tests

We now return to the issue discussed in section 5.5. Suppose that we have reason to doubt that $\mathbf{\Sigma}$ is of Type H. This may be because we do not believe that the limitations of the test for sphericity discussed in section 5.5 are too serious, and we have rejected the null hypothesis when performing this test. Alternatively, this may be because we question the assumption of Type H covariance to begin with as being unrealistic (more in a moment). In any event, we do not feel comfortable assuming that $\mathbf{\Sigma}$ is of Type H (thus, certainly does not exhibit **compound symmetry**, as stated by the model). Thus, the usual F tests for Time and Group by Time are invalid. Several suggestions are available for "adjusting" the usual F tests.

Define

$$\epsilon = \frac{\text{tr}^2(\boldsymbol{U}'\mathbf{\Sigma}\boldsymbol{U})}{(n-1)\text{tr}(\boldsymbol{U}'\mathbf{\Sigma}\boldsymbol{U}\boldsymbol{U}'\mathbf{\Sigma}\boldsymbol{U})},$$

where $\boldsymbol{U}$ is any $(n \times n-1)$ (so $u = n-1$) matrix whose columns are **normalized orthogonal contrasts**. It may be shown that the constant ϵ defined in this way must satisfy

$$1/(n-1) \leq \epsilon \leq 1$$

and that

$$\epsilon = 1$$

if, and only if, $\mathbf{\Sigma}$ is of Type H.

Because the usual F tests are too liberal (see above) if $\mathbf{\Sigma}$ is not of Type H, one suggestion is as follows. Rather than compare the F ratios to the usual critical values with a and b numerator and denominator degrees of freedom, say, compare them to F critical values with ϵa and ϵb numerator and denominator degrees of freedom instead. This will make the degrees of freedom **smaller** than usual. A quick look at a table of F critical values shows that, as the numerator and denominator degrees of freedom get smaller, the value of the critical value gets **larger**. Thus, the effect of this "adjustment" would be to compare F ratios to larger critical values, making it harder to reject the null hypothesis and thus making the test less **liberal**.

- Of course, ϵ is not known, because it depends on the unknown $\mathbf{\Sigma}$ matrix.
- Several approaches are based on **estimating $\mathbf{\Sigma}$** (to be discussed in the next chapter of the course) and then using the result to form an estimate for ϵ.

- This may be done in different ways; two such approaches are known as the **Greenhouse-Geisser** and **Huynh-Feldt** adjustments. Each estimates ϵ in a different way; the Huynh-Feldt estimate is such that the adjustment to the degrees of freedom is not as severe as that of the Greenhouse-Geisser adjustment. These adjustments are available in most software for analyzing repeated measurements; e.g. SAS `PROC GLM` computes the adjustments automatically, as we will see in the examples in section 5.8. They are, however, **approximate**.

- The general utility of these adjustments is unclear, however. That is, it is not necessarily the case that making the adjustments in a real situation where the numbers of units are small will indeed lead to valid tests.

SUMMARY: The spirit of the methods discussed above may be summarized as follows. One adopts a **statistical model** that makes a very specific assumption about associations among observations on the same unit (**compound symmetry**). If this assumption is correct, then familiar analysis of variance methods are available. It is possible to test whether it is correct; however, the testing procedures available are not too reliable. In the event that one doubts the compound symmetry assumption, approximate methods are available to still allow "adjusted" versions of the methods to be used. However, these adjustments are not necessarily reliable, either.

This suggests that, rather then try to "force" the issue of compound symmetry, a better approach might be to start back at the beginning, with a more realistic **statistical model**! In later chapters we will discuss other methods for analyzing longitudinal data that do not rely on the assumption of compound symmetry (or more generally, Type H covariance). We will also see that it is possible to adopt much more general representations for the form of the **mean** of a data vector.

5.8 Implementation with SAS

We consider two examples:

1. The dental study data. Here, $q = 2$ and $n = 4$, with the "time" factor being the age of the children and equally-spaced "time" points at 8, 10, 12, and 14 years of age.

2. the guinea pig diet data. Here, $q = 3$ and $n = 6$, with the "time" factor being weeks and unequally-spaced "time" points at 1, 3, 4, 5, 6, and 7 weeks.

In each case, we use SAS `PROC GLM` to carry out the computations. These examples thus serve to illustrate how this SAS procedure may be used to conduct univariate repeated measures analysis of variance.

Each program carries out construction of the analysis of variance table in two ways

- Using the same specification that would be used for the analysis of a **split plot** experiment
- Using the special `REPEATED` statement in `PROC GLM`. This statement and its associated options allow the user to request various specialized analyses, like those involving contrasts discussed in the last section. A full description of the features available may be found in the SAS documentation for `PROC GLM`.

EXAMPLE 1 – DENTAL STUDY DATA: The data are read in from the file `dental.dat`.

PROGRAM:

```
/*********************************************************************

  CHAPTER 5, EXAMPLE 1

  Analysis of the dental study data by repeated
  measures analysis of variance using PROC GLM

  -  the repeated measurement factor is age (time)

  -  there is one "treatment" factor, gender

*********************************************************************/

options ls=80 ps=59 nodate; run;

/*********************************************************************

  The data set looks like

1 1 8 21 0
2 1 10 20 0
3 1 12 21.5 0
4 1 14 23 0
5 2 8 21 0
      .
      .
      .

  column 1    observation number
  column 2    child id number
  column 3    age
  column 4    response (distance)
  column 5    gender indicator (0=girl, 1=boy)

  The second data step changes the ages from 8, 10, 12, 14
  to 1, 2, 3, 4 so that SAS can count them when it creates a
  different data set later

*********************************************************************/

data dent1; infile 'dental.dat';
  input obsno child age distance gender;
run;

data dent1; set dent1;
  if age=8 then age=1;
  if age=10 then age=2;
  if age=12 then age=3;
  if age=14 then age=4;
  drop obsno;
run;

/*********************************************************************

  Create an alternative data set with the data record for each child
  on a single line.

*********************************************************************/

proc sort data=dent1;
  by gender child;
data dent2(keep=age1-age4 gender);
  array aa{4} age1-age4;
  do age=1 to 4;
  set dent1;
  by gender child;
  aa{age}=distance;
  if last.child then return;
end;
run;

proc print;

/*********************************************************************

  Find the means of each gender-age combination and plot mean
  vs. age for each gender

*********************************************************************/

proc sort data=dent1; by gender age; run;
proc means data=dent1; by gender age;
  var distance;
  output out=mdent mean=mdist; run;
```

```
proc plot data=mdent; plot mdist*age=gender; run;

/*****************************************************************

  Construct the analysis of variance using PROC GLM
  via a "split plot" specification.  This requires that the
  data be represented in the form they are given in data set dent1.

  Note that the F ratio that PROC GLM prints out automatically
  for the gender effect (averaged across age) will use the
  MSE in the denominator.  This is not the correct F ratio for
  testing this effect.

  The RANDOM statement asks SAS to compute the expected mean
  squares for each source of variation.  The TEST option asks
  SAS to compute the test for the gender effect (averaged across
  age), treating the child(gender) effect as random, giving the
  correct F ratio.  Other F-ratios are correct.

  In older versions of SAS that do not recognize this option,
  this test could be obtained by removing the TEST option
  from the RANDOM statement and adding the statement

  test h=gender e = child(gender);

  to the call to PROC GLM.

*****************************************************************/

proc glm data=dent1;
  class age gender child;
  model distance = gender child(gender) age age*gender;
  random child(gender) / test;
run;

/*****************************************************************

  Now carry out the same analysis using the REPEATED statement in
  PROC GLM.  This requires that the data be represented in the
  form of data set dent2.

  The option NOUNI suppresses individual analyses of variance
  for the data at each age value from being printed.

  The PRINTE option asks for the test of sphericity to be performed.

  The NOM option means "no multivariate," which means just do
  the univariate repeated measures analysis under the assumption
  that the exchangable (compound symmetry) model is correct.

*****************************************************************/

proc glm data=dent2;
  class gender;
  model age1 age2 age3 age4 = gender / nouni;
  repeated age / printe nom;

/*****************************************************************

  This call to PROC GLM redoes the basic analysis of the last.
  However, in the REPEATED statement, a different contrast of
  the parameters is specified, the POLYNOMIAL transformation.
  The levels of "age" are equally spaced, and the values are
  specified.  The transformation produced is orthogonal polynomials
  for polynomial trends (linear, quadratic, cubic).

  The SUMMARY option asks that PROC GLM print out the results of
  tests corresponding to the contrasts in each column of the U
  matrix.

  The NOU option asks that printing of the univariate analysis
  of variance be suppressed (we already did it in the previous
  PROC GLM call).

  THE PRINTM option prints out the U matrix corresponding to the
  orthogonal polynomial contrasts.  SAS calls this matrix M, and
  actuallly prints out its transponse (our U').

  For the orthogonal polynomial transformation, SAS uses the
  normalized version of the U matrix.  Thus, the SSs from the
  individual ANOVAs for each column will add up to the Gender by
  Age interaction SS (and similarly for the within-unit error SS).

*****************************************************************/

proc glm data=dent2;
  class gender;
```

```
  model age1 age2 age3 age4 = gender / nouni;
  repeated age 4 (8 10 12 14) polynomial /summary nou nom printm;
run;

/*****************************************************************

  For comparison, we do the same analysis as above, but use the
  Helmert matrix instead.

  SAS does NOT use the normalized version of the Helmert
  transformation matrix.  Thus, the SSs from the individual ANOVAs
  for each column will NOT add up to the Gender by  Age interaction
  SS (similarly for within-unit error).  However, the F ratios
  are correct.

*****************************************************************/

proc glm data=dent2;
  class gender;
  model age1 age2 age3 age4 = gender / nouni;
  repeated age 4 (8 10 12 14) helmert /summary nou nom printm;
run;

/*****************************************************************

  Here, we manually perform the same analysis, but using the
  NORMALIZED version of the Helmert transformation matrix.
  We get each individual test separately using the PROC GLM
  MANOVA statement.

*****************************************************************/

proc glm data=dent2;
  model age1 age2 age3 age4 = gender /nouni;
  manova h=gender
m=0.866025404*age1 - 0.288675135*age2- 0.288675135*age3 - 0.288675135*age4;
manova h=gender m=  0.816496581*age2-0.40824829*age3-0.40824829*age4;
manova h=gender m=  0.707106781*age3-  0.707106781*age4;
run;

/*****************************************************************

  To compare, we apply the contrasts (normalized version) to each
  child's data.  We thus get a single value for each child corresponding
  to each contrast.  These are in the variables AGE1P -- AGE3P.
  We then use PROC GLM to perform each separate ANOVA.  It may be
  verified that the separate gender sums of squares add up to
  the interaction SS in the analysis above.

*****************************************************************/


data dent3; set dent2;
  age1p = sqrt(0.75)*(age1-age2/3-age3/3-age4/3);
  age2p = sqrt(2/3)*(age2-age3/2-age4/2);
  age3p = sqrt(1/2)*(age3-age4);
run;

proc glm; class gender; model age1p age2p age3p = gender;
run;
```

OUTPUT: One important note – it is important to always inspect the result of the Test for Sphericity using Mauchly's Criterion applied to Orthogonal Components. The test must be performed using an orthogonal, normalized transformation matrix. If the selected transformation (e.g. helmert) is not orthogonal **and** normalized, SAS will both do the test anyway, which is not appropriate, **and** do it using an orthogonal, normalized transformation, which is appropriate.

1

Obs	age1	age2	age3	age4	gender
1	21.0	20.0	21.5	23.0	0
2	21.0	21.5	24.0	25.5	0
3	20.5	24.0	24.5	26.0	0
4	23.5	24.5	25.0	26.5	0
5	21.5	23.0	22.5	23.5	0
6	20.0	21.0	21.0	22.5	0

```
                 7    21.5    22.5    23.0    25.0       0
                 8    23.0    23.0    23.5    24.0       0
                 9    20.0    21.0    22.0    21.5       0
                10    16.5    19.0    19.0    19.5       0
                11    24.5    25.0    28.0    28.0       0
                12    26.0    25.0    29.0    31.0       1
                13    21.5    22.5    23.0    26.5       1
                14    23.0    22.5    24.0    27.5       1
                15    25.5    27.5    26.5    27.0       1
                16    20.0    23.5    22.5    26.0       1
                17    24.5    25.5    27.0    28.5       1
                18    22.0    22.0    24.5    26.5       1
                19    24.0    21.5    24.5    25.5       1
                20    23.0    20.5    31.0    26.0       1
                21    27.5    28.0    31.0    31.5       1
                22    23.0    23.0    23.5    25.0       1
                23    21.5    23.5    24.0    28.0       1
                24    17.0    24.5    26.0    29.5       1
                25    22.5    25.5    25.5    26.0       1
                26    23.0    24.5    26.0    30.0       1
                27    22.0    21.5    23.5    25.0       1
                                                                                2

---------------------------------- gender=0 age=1 ----------------------------------

                           The MEANS Procedure

                        Analysis Variable : distance

        N            Mean         Std Dev         Minimum         Maximum
      ------------------------------------------------------------------
       11      21.1818182       2.1245320      16.5000000      24.5000000
      ------------------------------------------------------------------

---------------------------------- gender=0 age=2 ----------------------------------

                        Analysis Variable : distance

        N            Mean         Std Dev         Minimum         Maximum
      ------------------------------------------------------------------
       11      22.2272727       1.9021519      19.0000000      25.0000000
      ------------------------------------------------------------------

---------------------------------- gender=0 age=3 ----------------------------------

                        Analysis Variable : distance

        N            Mean         Std Dev         Minimum         Maximum
      ------------------------------------------------------------------
       11      23.0909091       2.3645103      19.0000000      28.0000000
      ------------------------------------------------------------------

---------------------------------- gender=0 age=4 ----------------------------------

                        Analysis Variable : distance

        N            Mean         Std Dev         Minimum         Maximum
      ------------------------------------------------------------------
       11      24.0909091       2.4373980      19.5000000      28.0000000
      ------------------------------------------------------------------

---------------------------------- gender=1 age=1 ----------------------------------

                        Analysis Variable : distance

        N            Mean         Std Dev         Minimum         Maximum
      ------------------------------------------------------------------
       16      22.8750000       2.4528895      17.0000000      27.5000000
      ------------------------------------------------------------------

                                                                                3

---------------------------------- gender=1 age=2 ----------------------------------
                           The MEANS Procedure

                        Analysis Variable : distance

        N            Mean         Std Dev         Minimum         Maximum
      ------------------------------------------------------------------
       16      23.8125000       2.1360009      20.5000000      28.0000000
      ------------------------------------------------------------------

---------------------------------- gender=1 age=3 ----------------------------------

                        Analysis Variable : distance

        N            Mean         Std Dev         Minimum         Maximum
      ------------------------------------------------------------------
       16      25.7187500       2.6518468      22.5000000      31.0000000
```

```
-------------------------------------------------------------------

-------------------------------- gender=1 age=4 --------------------------------

                        Analysis Variable : distance

        N            Mean         Std Dev         Minimum         Maximum
     ----------------------------------------------------------------------
     16      27.4687500       2.0854156      25.0000000      31.5000000
     ----------------------------------------------------------------------
                                                                          4

                Plot of mdist*age.  Symbol is value of gender.

     mdist |
           |
        28 +
           |
           |                                                        1
           |
           |
        27 +
           |
           |
           |
           |
           |
        26 +
           |                                     1
           |
           |
           |
        25 +
           |
           |
           |
           |                                                        0
        24 +
           |                     1
           |
           |
           |                                     0
        23 +
           |  1
           |
           |
           |
           |                     0
        22 +
           |
           |
           |
           |
           |  0
        21 +
           |
           ---+-----------------+-----------------+-----------------+--
              1                 2                 3                 4

                                       age
                                                                          5

                             The GLM Procedure

                          Class Level Information

Class       Levels  Values

age              4  1 2 3 4
gender           2  0 1
child           27  1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
                    24 25 26 27

                          Number of observations    108

                                                                          6

                             The GLM Procedure

Dependent Variable: distance

 Source                      DF        Sum of
                                      Squares    Mean Square   F Value   Pr > F

 Model                       32    769.5642887     24.0488840     12.18   <.0001
```

```
Error                       75    148.1278409      1.9750379

Corrected Total            107    917.6921296

            R-Square     Coeff Var      Root MSE    distance Mean

            0.838587      5.850026      1.405360         24.02315

Source                      DF      Type I SS    Mean Square   F Value   Pr > F

gender                       1    140.4648569    140.4648569     71.12   <.0001
child(gender)               25    377.9147727     15.1165909      7.65   <.0001
age                          3    237.1921296     79.0640432     40.03   <.0001
age*gender                   3     13.9925295      4.6641765      2.36   0.0781

Source                      DF    Type III SS    Mean Square   F Value   Pr > F

gender                       1    140.4648569    140.4648569     71.12   <.0001
child(gender)               25    377.9147727     15.1165909      7.65   <.0001
age                          3    209.4369739     69.8123246     35.35   <.0001
age*gender                   3     13.9925295      4.6641765      2.36   0.0781
                                                                          7

                              The GLM Procedure

Source                  Type III Expected Mean Square

gender                  Var(Error) + 4 Var(child(gender)) + Q(gender,age*gender)

child(gender)           Var(Error) + 4 Var(child(gender))
age                     Var(Error) + Q(age,age*gender)

age*gender              Var(Error) + Q(age*gender)
                                                                          8

                              The GLM Procedure
           Tests of Hypotheses for Mixed Model Analysis of Variance

Dependent Variable: distance

     Source                     DF   Type III SS   Mean Square  F Value  Pr > F

  *  gender                      1    140.464857    140.464857     9.29  0.0054

     Error                      25    377.914773     15.116591
  Error: MS(child(gender))

  * This test assumes one or more other fixed effects are zero.

     Source                     DF   Type III SS   Mean Square  F Value  Pr > F

     child(gender)              25    377.914773     15.116591     7.65  <.0001
  *  age                         3    209.436974     69.812325    35.35  <.0001
     age*gender                  3     13.992529      4.664176     2.36  0.0781

     Error: MS(Error)           75    148.127841      1.975038

  * This test assumes one or more other fixed effects are zero.
                                                                          9

                              The GLM Procedure

                          Class Level Information

                        Class         Levels    Values

                        gender             2    0 1

                         Number of observations    27
                                                                         10

                              The GLM Procedure
                     Repeated Measures Analysis of Variance

                      Repeated Measures Level Information

           Dependent Variable        age1     age2     age3     age4

                 Level of age           1        2        3        4

    Partial Correlation Coefficients from the Error SSCP Matrix / Prob > |r|

      DF = 25           age1           age2           age3           age4

      age1          1.000000       0.570699       0.661320       0.521583
                                     0.0023         0.0002         0.0063

      age2          0.570699       1.000000       0.563167       0.726216
```

	0.0023		0.0027	<.0001
age3	0.661320	0.563167	1.000000	0.728098
	0.0002	0.0027		<.0001
age4	0.521583	0.726216	0.728098	1.000000
	0.0063	<.0001	<.0001	

E = Error SSCP Matrix

age_N represents the contrast between the nth level of age and the last

	age_1	age_2	age_3
age_1	124.518	41.879	51.375
age_2	41.879	63.405	11.625
age_3	51.375	11.625	79.500

Partial Correlation Coefficients from the Error SSCP Matrix of the Variables Defined by the Specified Transformation / Prob > |r|

DF = 25	age_1	age_2	age_3
age_1	1.000000	0.471326	0.516359
		0.0151	0.0069
age_2	0.471326	1.000000	0.163738
	0.0151		0.4241
age_3	0.516359	0.163738	1.000000
	0.0069	0.4241	

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The GLM Procedure
Repeated Measures Analysis of Variance

Sphericity Tests

Variables	DF	Mauchly's Criterion	Chi-Square	Pr > ChiSq
Transformed Variates	5	0.4998695	16.449181	0.0057
Orthogonal Components	5	0.7353334	7.2929515	0.1997

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The GLM Procedure
Repeated Measures Analysis of Variance
Tests of Hypotheses for Between Subjects Effects

Source	DF	Type III SS	Mean Square	F Value	Pr > F
gender	1	140.4648569	140.4648569	9.29	0.0054
Error	25	377.9147727	15.1165909		

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The GLM Procedure
Repeated Measures Analysis of Variance
Univariate Tests of Hypotheses for Within Subject Effects

Source	DF	Type III SS	Mean Square	F Value	Pr > F
age	3	209.4369739	69.8123246	35.35	<.0001
age*gender	3	13.9925295	4.6641765	2.36	0.0781
Error(age)	75	148.1278409	1.9750379		

Source	Adj Pr > F G - G	H - F
age	<.0001	<.0001
age*gender	0.0878	0.0781
Error(age)		

Greenhouse-Geisser Epsilon	0.8672
Huynh-Feldt Epsilon	1.0156

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The GLM Procedure

Class Level Information

Class	Levels	Values
gender	2	0 1

Number of observations 27

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The GLM Procedure
Repeated Measures Analysis of Variance

Repeated Measures Level Information

Dependent Variable	age1	age2	age3	age4
Level of age	8	10	12	14

age_N represents the nth degree polynomial contrast for age

M Matrix Describing Transformed Variables

	age1	age2	age3	age4
age_1	-.6708203932	-.2236067977	0.2236067977	0.6708203932
age_2	0.5000000000	-.5000000000	-.5000000000	0.5000000000
age_3	-.2236067977	0.6708203932	-.6708203932	0.2236067977

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The GLM Procedure
Repeated Measures Analysis of Variance
Tests of Hypotheses for Between Subjects Effects

Source	DF	Type III SS	Mean Square	F Value	Pr > F
gender	1	140.4648569	140.4648569	9.29	0.0054
Error	25	377.9147727	15.1165909		

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The GLM Procedure
Repeated Measures Analysis of Variance
Analysis of Variance of Contrast Variables

age_N represents the nth degree polynomial contrast for age

Contrast Variable: age_1

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Mean	1	208.2660038	208.2660038	88.00	<.0001
gender	1	12.1141519	12.1141519	5.12	0.0326
Error	25	59.1673295	2.3666932		

Contrast Variable: age_2

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Mean	1	0.95880682	0.95880682	0.92	0.3465
gender	1	1.19954756	1.19954756	1.15	0.2935
Error	25	26.04119318	1.04164773		

Contrast Variable: age_3

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Mean	1	0.21216330	0.21216330	0.08	0.7739
gender	1	0.67882997	0.67882997	0.27	0.6081
Error	25	62.91931818	2.51677273		

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The GLM Procedure

Class Level Information

Class	Levels	Values
gender	2	0 1

Number of observations 27

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The GLM Procedure
Repeated Measures Analysis of Variance

Repeated Measures Level Information

Dependent Variable	age1	age2	age3	age4

```
                Level of age           8       10       12       14

                age_N represents the contrast between the nth
                level of age and the mean of subsequent levels

                  M Matrix Describing Transformed Variables

                   age1              age2              age3              age4

 age_1       1.000000000      -0.333333333      -0.333333333      -0.333333333
 age_2       0.000000000       1.000000000      -0.500000000      -0.500000000
 age_3       0.000000000       0.000000000       1.000000000      -1.000000000
```

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```
                            The GLM Procedure
                     Repeated Measures Analysis of Variance
                 Tests of Hypotheses for Between Subjects Effects

 Source                     DF    Type III SS    Mean Square   F Value   Pr > F

 gender                      1    140.4648569    140.4648569      9.29   0.0054
 Error                      25    377.9147727     15.1165909
```

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```
                            The GLM Procedure
                     Repeated Measures Analysis of Variance
                   Analysis of Variance of Contrast Variables

age_N represents the contrast between the nth level of age and the mean of
subsequent levels

Contrast Variable: age_1

 Source                     DF    Type III SS    Mean Square   F Value   Pr > F

 Mean                        1    146.8395997    146.8395997     45.43   <.0001
 gender                      1      4.5679948      4.5679948      1.41   0.2457
 Error                      25     80.8106061      3.2324242


Contrast Variable: age_2

 Source                     DF    Type III SS    Mean Square   F Value   Pr > F

 Mean                        1    111.9886890    111.9886890     39.07   <.0001
 gender                      1     13.0998001     13.0998001      4.57   0.0425
 Error                      25     71.6548295      2.8661932


Contrast Variable: age_3

 Source                     DF    Type III SS    Mean Square   F Value   Pr > F

 Mean                        1    49.29629630    49.29629630     15.50   0.0006
 gender                      1     3.66666667     3.66666667      1.15   0.2932
 Error                      25    79.50000000     3.18000000
```

22

```
                               The GLM Procedure

                          Number of observations    27
```

23

```
                            The GLM Procedure
                        Multivariate Analysis of Variance

                  M Matrix Describing Transformed Variables

                   age1              age2              age3              age4

 MVAR1       0.866025404      -0.288675135      -0.288675135      -0.288675135
```

24

```
                            The GLM Procedure
                        Multivariate Analysis of Variance

          Characteristic Roots and Vectors of: E Inverse * H, where
                    H = Type III SSCP Matrix for gender
                          E = Error SSCP Matrix

               Variables have been transformed by the M Matrix

                  Characteristic              Characteristic Vector  V'EV=1
                            Root    Percent           MVAR1
```

```
                    0.05652717     100.00      0.12845032


               MANOVA Test Criteria and Exact F Statistics for
                  the Hypothesis of No Overall gender Effect
            on the Variables Defined by the M Matrix Transformation
                  H = Type III SSCP Matrix for gender
                         E = Error SSCP Matrix

                          S=1    M=-0.5    N=11.5

Statistic                        Value    F Value    Num DF    Den DF    Pr > F

Wilks' Lambda                0.94649719       1.41         1        25    0.2457
Pillai's Trace               0.05350281       1.41         1        25    0.2457
Hotelling-Lawley Trace       0.05652717       1.41         1        25    0.2457
Roy's Greatest Root          0.05652717       1.41         1        25    0.2457

                                                                          25

                          The GLM Procedure
                    Multivariate Analysis of Variance

                  M Matrix Describing Transformed Variables

                   age1              age2              age3              age4

 MVAR1                0       0.816496581       -0.40824829       -0.40824829

                                                                          26

                          The GLM Procedure
                    Multivariate Analysis of Variance

          Characteristic Roots and Vectors of: E Inverse * H, where
                  H = Type III SSCP Matrix for gender
                         E = Error SSCP Matrix

               Variables have been transformed by the M Matrix

                  Characteristic              Characteristic Vector  V'EV=1
                            Root    Percent           MVAR1

                    0.18281810     100.00      0.14468480


               MANOVA Test Criteria and Exact F Statistics for
                  the Hypothesis of No Overall gender Effect
            on the Variables Defined by the M Matrix Transformation
                  H = Type III SSCP Matrix for gender
                         E = Error SSCP Matrix

                          S=1    M=-0.5    N=11.5

Statistic                        Value    F Value    Num DF    Den DF    Pr > F

Wilks' Lambda                0.84543853       4.57         1        25    0.0425
Pillai's Trace               0.15456147       4.57         1        25    0.0425
Hotelling-Lawley Trace       0.18281810       4.57         1        25    0.0425
Roy's Greatest Root          0.18281810       4.57         1        25    0.0425

                                                                          27

                          The GLM Procedure
                    Multivariate Analysis of Variance

                  M Matrix Describing Transformed Variables

                   age1              age2              age3              age4

 MVAR1                0                 0       0.707106781      -0.707106781

                                                                          28

                          The GLM Procedure
                    Multivariate Analysis of Variance

          Characteristic Roots and Vectors of: E Inverse * H, where
                  H = Type III SSCP Matrix for gender
                         E = Error SSCP Matrix

               Variables have been transformed by the M Matrix

                  Characteristic              Characteristic Vector  V'EV=1
                            Root    Percent           MVAR1

                    0.04612159     100.00      0.15861032
```

MANOVA Test Criteria and Exact F Statistics for
the Hypothesis of No Overall gender Effect
on the Variables Defined by the M Matrix Transformation
H = Type III SSCP Matrix for gender
E = Error SSCP Matrix

S=1 M=-0.5 N=11.5

Statistic	Value	F Value	Num DF	Den DF	Pr > F
Wilks' Lambda	0.95591182	1.15	1	25	0.2932
Pillai's Trace	0.04408818	1.15	1	25	0.2932
Hotelling-Lawley Trace	0.04612159	1.15	1	25	0.2932
Roy's Greatest Root	0.04612159	1.15	1	25	0.2932

29

The GLM Procedure

Class Level Information

Class	Levels	Values
gender	2	0 1

Number of observations 27

30

The GLM Procedure

Dependent Variable: age1p

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	1	3.42599607	3.42599607	1.41	0.2457
Error	25	60.60795455	2.42431818		
Corrected Total	26	64.03395062			

R-Square	Coeff Var	Root MSE	age1p Mean
0.053503	-73.36496	1.557022	-2.122297

Source	DF	Type I SS	Mean Square	F Value	Pr > F
gender	1	3.42599607	3.42599607	1.41	0.2457

Source	DF	Type III SS	Mean Square	F Value	Pr > F
gender	1	3.42599607	3.42599607	1.41	0.2457

31

The GLM Procedure

Dependent Variable: age2p

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	1	8.73320006	8.73320006	4.57	0.0425
Error	25	47.76988636	1.91079545		
Corrected Total	26	56.50308642			

R-Square	Coeff Var	Root MSE	age2p Mean
0.154561	-76.82446	1.382315	-1.799317

Source	DF	Type I SS	Mean Square	F Value	Pr > F
gender	1	8.73320006	8.73320006	4.57	0.0425

Source	DF	Type III SS	Mean Square	F Value	Pr > F
gender	1	8.73320006	8.73320006	4.57	0.0425

32

The GLM Procedure

Dependent Variable: age3p

```
 Source                     DF       Sum of Squares    Mean Square   F Value   Pr > F
 Model                       1     1.83333333      1.83333333       1.15   0.2932
 Error                      25    39.75000000      1.59000000
 Corrected Total            26    41.58333333

               R-Square     Coeff Var      Root MSE    age3p Mean
               0.044088     -123.4561      1.260952     -1.021376

 Source                     DF      Type I SS    Mean Square   F Value   Pr > F
 gender                      1     1.83333333      1.83333333       1.15   0.2932
 Source                     DF    Type III SS    Mean Square   F Value   Pr > F
 gender                      1     1.83333333      1.83333333       1.15   0.2932
```

EXAMPLE 2 – GUINEA PIG DIET DATA: The data are read in from the file `diet.dat`.

PROGRAM:

```
/*********************************************************************

  CHAPTER 5, EXAMPLE 2

  Analysis of the vitamin E data by univariate repeated
  measures analysis of variance using PROC GLM

  -  the repeated measurement factor is week (time)

  -  there is one "treatment" factor, dose

*********************************************************************/

options ls=80 ps=59 nodate; run;

/*********************************************************************

  The data set looks like

1 455 460 510 504 436 466  1
2 467 565 610 596 542 587  1
3 445 530 580 597 582 619  1
4 485 542 594 583 611 612  1
5 480 500 550 528 562 576  1
6 514 560 565 524 552 597  2
7 440 480 536 484 567 569  2
8 495 570 569 585 576 677  2
9 520 590 610 637 671 702  2
10 503 555 591 605 649 675  2
11 496 560 622 622 632 670  3
12 498 540 589 557 568 609  3
13 478 510 568 555 576 605  3
14 545 565 580 601 633 649  3
15 472 498 540 524 532 583  3

  column 1      pig number
  columns 2-7   body weights at weeks 1, 3, 4, 5, 6, 7
  column 8      dose group  (1=zero, 2 = low, 3 = high dose

*********************************************************************/

data pigs1; infile 'diet.dat';
  input pig week1 week3 week4 week5 week6 week7 dose;

/*********************************************************************

  Create a data set with one data record per pig/week -- this
  repeated measures data are often recorded in this form.

  Create a new variable "weight" containing the body weight
  at time "week."

  The second data step fixes up the "week" values, as the weeks
  of observations were not equally spaced but rather have the
  values 1, 3, 4, 5, 6, 7.

*********************************************************************/
```

```
data pigs2; set pigs1;
  array wt(6) week1 week3 week4 week5 week6 week7;
  do week = 1 to 6;
     weight = wt(week);
     output;
  end;
  drop week1 week3-week7;
run;

data pigs2; set pigs2;
  if week>1 then week=week+1;
run;

proc print; run;

/*********************************************************************

  Find the means of each dose-week combination and plot mean
  vs. week for each dose;

*********************************************************************/

proc sort data=pigs2; by dose week; run;
proc means data=pigs2; by dose week;
  var weight;
  output out=mpigs mean=mweight; run;

proc plot data=mpigs; plot mweight*week=dose; run;

/*********************************************************************

  First construct the analysis of variance using PROC GLM
  via a "split plot" specification.  This requires that the
  data be represented in the form they are given in data set pigs2.

  Note that the F ratio that PROC GLM prints out automatically
  for the dose effect (averaged across week) will use the
  MSE in the denominator.  This is not the correct F ratio for
  testing this effect.

  The RANDOM statement asks SAS to compute the expected mean
  squares for each source of variation.  The TEST option asks
  SAS to compute the test for the dose effect (averaged across
  week), treating the pig(dose) effect as random, giving the
  correct F ratio.  Other F-ratios are correct.

  In older versions of SAS that do not recognize this option,
  this test could be obtained by removing the TEST option
  from the RANDOM statement and adding the statement

  test h=dose e=pig(gender)

  to the call to PROC GLM.

*********************************************************************/

proc glm data=pigs2;
  class week dose pig;
  model weight = dose pig(dose) week week*dose;
  random pig(dose) / test;
run;

/*********************************************************************

  Now carry out the same analysis using the REPEATED statement in
  PROC GLM.  This requires that the data be represented in the
  form of data set pigs1.

  The option NOUNI suppresses individual analyses of variance
  at each week value from being printed.

  The PRINTE option asks for the test of sphericity to be performed.

  The NOM option means "no multivariate," which means univariate
  tests under the assumption that the compound symmetry model
  is correct.

*********************************************************************/

proc glm data=pigs1;
  class dose;
  model week1 week3 week4 week5 week6 week7 = dose / nouni;
  repeated week / printe nom;
run;

/*********************************************************************

  These calls to PROC GLM redo the basic analysis of the last.
```

```
  However, in the REPEATED statement, different contrasts of
  the parameters are specified.

  The SUMMARY option asks that PROC GLM print out the results of
  tests corresponding to the contrasts in each column of the U
  matrix.

  The NOU option asks that printing of the univariate analysis
  of variance be suppressed (we already did it in the previous
  PROC GLM call).

  THE PRINTM option prints out the U matrix corresponding to the
  contrasts being used .  SAS calls this matrix M, and
  actually prints out its transpose (our U').

*****************************************************************/

proc glm data=pigs1;
  class dose;
  model week1 week3 week4 week5 week6 week7 = dose / nouni;
  repeated week 6 (1 3 4 5 6 7) polynomial /summary printm nom;
run;

proc glm data=pigs1;
  class dose;
  model week1 week3 week4 week5 week6 week7 = dose / nouni;
  repeated week 6 (1 3 4 5 6 7) profile /summary printm nom ;
run;

proc glm data=pigs1;
  class dose;
  model week1 week3 week4 week5 week6 week7 = dose / nouni;
  repeated week 6  helmert /summary printm nom;
run;
```

OUTPUT: The same warning about the test for sphericity applies here.

1

Obs	pig	dose	week	weight
1	1	1	1	455
2	1	1	3	460
3	1	1	4	510
4	1	1	5	504
5	1	1	6	436
6	1	1	7	466
7	2	1	1	467
8	2	1	3	565
9	2	1	4	610
10	2	1	5	596
11	2	1	6	542
12	2	1	7	587
13	3	1	1	445
14	3	1	3	530
15	3	1	4	580
16	3	1	5	597
17	3	1	6	582
18	3	1	7	619
19	4	1	1	485
20	4	1	3	542
21	4	1	4	594
22	4	1	5	583
23	4	1	6	611
24	4	1	7	612
25	5	1	1	480
26	5	1	3	500
27	5	1	4	550
28	5	1	5	528
29	5	1	6	562
30	5	1	7	576
31	6	2	1	514
32	6	2	3	560
33	6	2	4	565
34	6	2	5	524
35	6	2	6	552
36	6	2	7	597
37	7	2	1	440
38	7	2	3	480
39	7	2	4	536
40	7	2	5	484
41	7	2	6	567
42	7	2	7	569
43	8	2	1	495
44	8	2	3	570
45	8	2	4	569
46	8	2	5	585

47	8	2	6	576
48	8	2	7	677
49	9	2	1	520
50	9	2	3	590
51	9	2	4	610
52	9	2	5	637
53	9	2	6	671
54	9	2	7	702
55	10	2	1	503

2

Obs	pig	dose	week	weight
56	10	2	3	555
57	10	2	4	591
58	10	2	5	605
59	10	2	6	649
60	10	2	7	675
61	11	3	1	496
62	11	3	3	560
63	11	3	4	622
64	11	3	5	622
65	11	3	6	632
66	11	3	7	670
67	12	3	1	498
68	12	3	3	540
69	12	3	4	589
70	12	3	5	557
71	12	3	6	568
72	12	3	7	609
73	13	3	1	478
74	13	3	3	510
75	13	3	4	568
76	13	3	5	555
77	13	3	6	576
78	13	3	7	605
79	14	3	1	545
80	14	3	3	565
81	14	3	4	580
82	14	3	5	601
83	14	3	6	633
84	14	3	7	649
85	15	3	1	472
86	15	3	3	498
87	15	3	4	540
88	15	3	5	524
89	15	3	6	532
90	15	3	7	583

3

---------- dose=1 week=1 ----------

The MEANS Procedure

Analysis Variable : weight

N	Mean	Std Dev	Minimum	Maximum
5	466.4000000	16.7272233	445.0000000	485.0000000

---------- dose=1 week=3 ----------

Analysis Variable : weight

N	Mean	Std Dev	Minimum	Maximum
5	519.4000000	40.6423425	460.0000000	565.0000000

---------- dose=1 week=4 ----------

Analysis Variable : weight

N	Mean	Std Dev	Minimum	Maximum
5	568.8000000	39.5878769	510.0000000	610.0000000

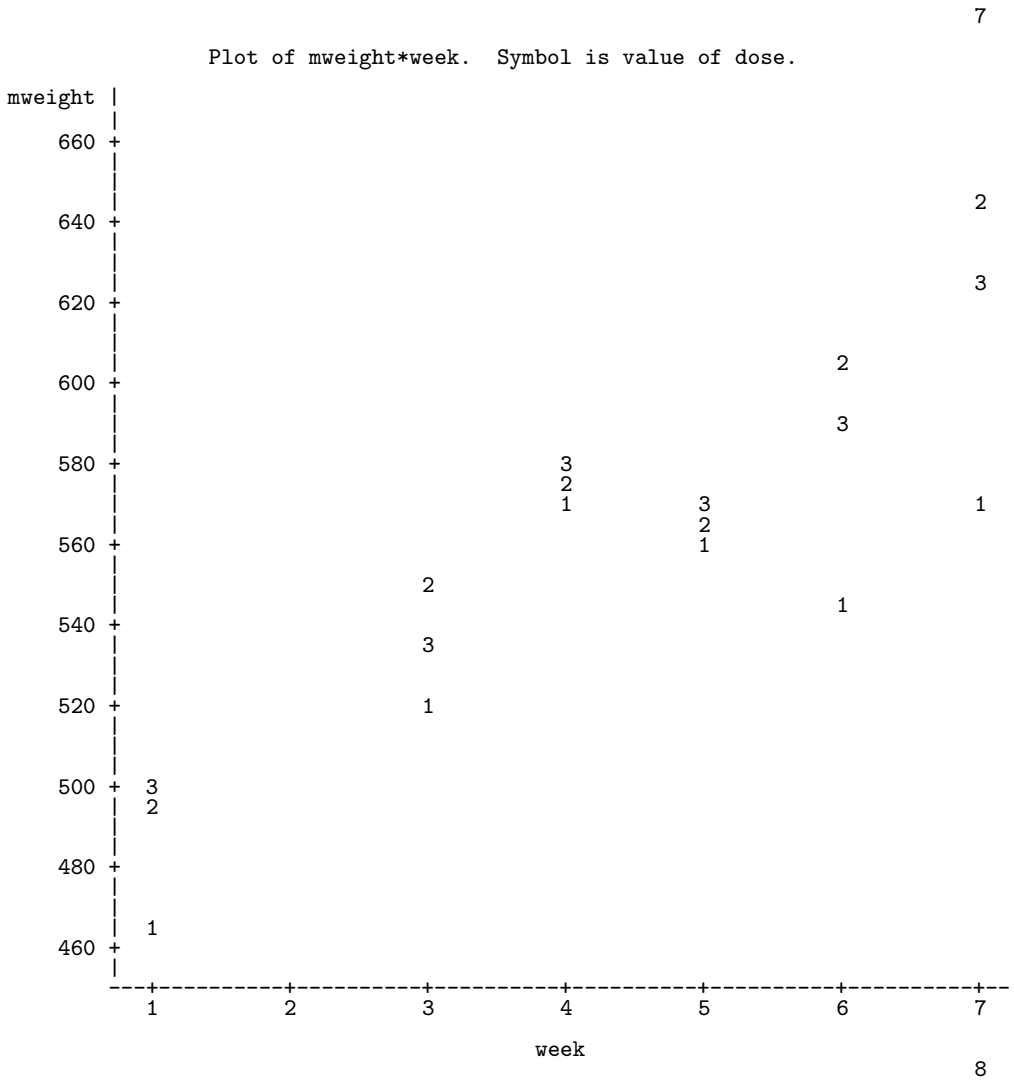
---------- dose=1 week=5 ----------

Analysis Variable : weight

N	Mean	Std Dev	Minimum	Maximum
5	561.6000000	42.8404015	504.0000000	597.0000000

```
-------------------------------- dose=1 week=6 --------------------------------

                          Analysis Variable : weight

        N            Mean         Std Dev         Minimum         Maximum
       ---------------------------------------------------------------------
       5     546.6000000      66.8789952     436.0000000     611.0000000
       ---------------------------------------------------------------------

                                                                          4
-------------------------------- dose=1 week=7 --------------------------------

                             The MEANS Procedure

                          Analysis Variable : weight

        N            Mean         Std Dev         Minimum         Maximum
       ---------------------------------------------------------------------
       5     572.0000000      61.8182821     466.0000000     619.0000000
       ---------------------------------------------------------------------

-------------------------------- dose=2 week=1 --------------------------------

                          Analysis Variable : weight

        N            Mean         Std Dev         Minimum         Maximum
       ---------------------------------------------------------------------
       5     494.4000000      31.9108132     440.0000000     520.0000000
       ---------------------------------------------------------------------

-------------------------------- dose=2 week=3 --------------------------------

                          Analysis Variable : weight

        N            Mean         Std Dev         Minimum         Maximum
       ---------------------------------------------------------------------
       5     551.0000000      41.8927201     480.0000000     590.0000000
       ---------------------------------------------------------------------

-------------------------------- dose=2 week=4 --------------------------------

                          Analysis Variable : weight

        N            Mean         Std Dev         Minimum         Maximum
       ---------------------------------------------------------------------
       5     574.2000000      27.9946423     536.0000000     610.0000000
       ---------------------------------------------------------------------

-------------------------------- dose=2 week=5 --------------------------------

                          Analysis Variable : weight

        N            Mean         Std Dev         Minimum         Maximum
       ---------------------------------------------------------------------
       5     567.0000000      62.0604544     484.0000000     637.0000000
       ---------------------------------------------------------------------

                                                                          5
-------------------------------- dose=2 week=6 --------------------------------

                             The MEANS Procedure

                          Analysis Variable : weight

        N            Mean         Std Dev         Minimum         Maximum
       ---------------------------------------------------------------------
       5     603.0000000      53.3057220     552.0000000     671.0000000
       ---------------------------------------------------------------------

-------------------------------- dose=2 week=7 --------------------------------

                          Analysis Variable : weight

        N            Mean         Std Dev         Minimum         Maximum
       ---------------------------------------------------------------------
       5     644.0000000      57.5499783     569.0000000     702.0000000
       ---------------------------------------------------------------------
```

```
-------------------------------- dose=3 week=1 --------------------------------

                        Analysis Variable : weight

        N            Mean         Std Dev         Minimum         Maximum
       ---------------------------------------------------------------------
        5     497.8000000      28.6740301     472.0000000     545.0000000
       ---------------------------------------------------------------------

-------------------------------- dose=3 week=3 --------------------------------

                        Analysis Variable : weight

        N            Mean         Std Dev         Minimum         Maximum
       ---------------------------------------------------------------------
        5     534.6000000      29.7623924     498.0000000     565.0000000
       ---------------------------------------------------------------------

-------------------------------- dose=3 week=4 --------------------------------

                        Analysis Variable : weight

        N            Mean         Std Dev         Minimum         Maximum
       ---------------------------------------------------------------------
        5     579.8000000      29.9532970     540.0000000     622.0000000
       ---------------------------------------------------------------------

                                                                          6
-------------------------------- dose=3 week=5 --------------------------------

                           The MEANS Procedure

                        Analysis Variable : weight

        N            Mean         Std Dev         Minimum         Maximum
       ---------------------------------------------------------------------
        5     571.8000000      39.2390112     524.0000000     622.0000000
       ---------------------------------------------------------------------

-------------------------------- dose=3 week=6 --------------------------------

                        Analysis Variable : weight

        N            Mean         Std Dev         Minimum         Maximum
       ---------------------------------------------------------------------
        5     588.2000000      43.7058349     532.0000000     633.0000000
       ---------------------------------------------------------------------

-------------------------------- dose=3 week=7 --------------------------------

                        Analysis Variable : weight

        N            Mean         Std Dev         Minimum         Maximum
       ---------------------------------------------------------------------
        5     623.2000000      35.3723056     583.0000000     670.0000000
       ---------------------------------------------------------------------
```



8

The GLM Procedure

Class Level Information

Class	Levels	Values
week	6	1 3 4 5 6 7
dose	3	1 2 3
pig	15	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Number of observations 90

9

The GLM Procedure

Dependent Variable: weight

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	29	276299.5000	9527.5690	17.56	<.0001
Error	60	32552.6000	542.5433		
Corrected Total	89	308852.1000			

R-Square	Coeff Var	Root MSE	weight Mean
0.894601	4.166081	23.29256	559.1000

Source	DF	Type I SS	Mean Square	F Value	Pr > F

dose	2	18548.0667	9274.0333	17.09	<.0001
pig(dose)	12	105434.2000	8786.1833	16.19	<.0001
week	5	142554.5000	28510.9000	52.55	<.0001
week*dose	10	9762.7333	976.2733	1.80	0.0801

Source	DF	Type III SS	Mean Square	F Value	Pr > F
dose	2	18548.0667	9274.0333	17.09	<.0001
pig(dose)	12	105434.2000	8786.1833	16.19	<.0001
week	5	142554.5000	28510.9000	52.55	<.0001
week*dose	10	9762.7333	976.2733	1.80	0.0801

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The GLM Procedure

Source	Type III Expected Mean Square
dose	Var(Error) + 6 Var(pig(dose)) + Q(dose,week*dose)
pig(dose)	Var(Error) + 6 Var(pig(dose))
week	Var(Error) + Q(week,week*dose)
week*dose	Var(Error) + Q(week*dose)

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The GLM Procedure
Tests of Hypotheses for Mixed Model Analysis of Variance

Dependent Variable: weight

	Source	DF	Type III SS	Mean Square	F Value	Pr > F
*	dose	2	18548	9274.033333	1.06	0.3782
	Error: MS(pig(dose))	12	105434	8786.183333		

* This test assumes one or more other fixed effects are zero.

	Source	DF	Type III SS	Mean Square	F Value	Pr > F
	pig(dose)	12	105434	8786.183333	16.19	<.0001
*	week	5	142555	28511	52.55	<.0001
	week*dose	10	9762.733333	976.273333	1.80	0.0801
	Error: MS(Error)	60	32553	542.543333		

* This test assumes one or more other fixed effects are zero.

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The GLM Procedure

Class Level Information

Class	Levels	Values
dose	3	1 2 3

Number of observations 15

13

The GLM Procedure
Repeated Measures Analysis of Variance

Repeated Measures Level Information

Dependent Variable	week1	week3	week4	week5	week6	week7
Level of week	1	2	3	4	5	6

Partial Correlation Coefficients from the Error SSCP Matrix / Prob > |r|

DF = 12	week1	week3	week4	week5	week6	week7
week1	1.000000	0.707584 0.0068	0.459151 0.1145	0.543739 0.0548	0.492366 0.0874	0.502098 0.0804
week3	0.707584 0.0068	1.000000	0.889996 <.0001	0.874228 <.0001	0.676753 0.0111	0.834899 0.0004
week4	0.459151 0.1145	0.889996 <.0001	1.000000	0.881217 <.0001	0.789575 0.0013	0.847786 0.0003

week5	0.543739	0.874228	0.881217	1.000000	0.803051	0.919350
	0.0548	<.0001	<.0001		0.0009	<.0001
week6	0.492366	0.676753	0.789575	0.803051	1.000000	0.895603
	0.0874	0.0111	0.0013	0.0009		<.0001
week7	0.502098	0.834899	0.847786	0.919350	0.895603	1.000000
	0.0804	0.0004	0.0003	<.0001	<.0001	

E = Error SSCP Matrix

week_N represents the contrast between the nth level of week and the last

	week_1	week_2	week_3	week_4	week_5
week_1	25083.6	13574.0	12193.2	4959.0	2274.8
week_2	13574.0	10638.4	9099.2	4354.6	-968.2
week_3	12193.2	9099.2	11136.8	4293.8	1623.6
week_4	4959.0	4354.6	4293.8	5194.4	-365.8
week_5	2274.8	-968.2	1623.6	-365.8	7425.2

The GLM Procedure
Repeated Measures Analysis of Variance

Partial Correlation Coefficients from the Error SSCP Matrix of the Variables Defined by the Specified Transformation / Prob > |r|

DF = 12	week_1	week_2	week_3	week_4	week_5
week_1	1.000000	0.830950	0.729529	0.434442	0.166684
		0.0004	0.0047	0.1380	0.5863
week_2	0.830950	1.000000	0.835959	0.585791	-0.108936
	0.0004		0.0004	0.0354	0.7231
week_3	0.729529	0.835959	1.000000	0.564539	0.178544
	0.0047	0.0004		0.0444	0.5595
week_4	0.434442	0.585791	0.564539	1.000000	-0.058901
	0.1380	0.0354	0.0444		0.8484
week_5	0.166684	-0.108936	0.178544	-0.058901	1.000000
	0.5863	0.7231	0.5595	0.8484	

Sphericity Tests

Variables	DF	Mauchly's Criterion	Chi-Square	Pr > ChiSq
Transformed Variates	14	0.0160527	41.731963	0.0001
Orthogonal Components	14	0.0544835	29.389556	0.0093

The GLM Procedure
Repeated Measures Analysis of Variance
Tests of Hypotheses for Between Subjects Effects

Source	DF	Type III SS	Mean Square	F Value	Pr > F
dose	2	18548.0667	9274.0333	1.06	0.3782
Error	12	105434.2000	8786.1833		

The GLM Procedure
Repeated Measures Analysis of Variance
Univariate Tests of Hypotheses for Within Subject Effects

Source	DF	Type III SS	Mean Square	F Value	Pr > F
week	5	142554.5000	28510.9000	52.55	<.0001
week*dose	10	9762.7333	976.2733	1.80	0.0801
Error(week)	60	32552.6000	542.5433		

Source	Adj Pr > F G - G	H - F
week	<.0001	<.0001
week*dose	0.1457	0.1103
Error(week)		

Greenhouse-Geisser Epsilon	0.4856
Huynh-Feldt Epsilon	0.7191

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The GLM Procedure

Class Level Information

Class	Levels	Values
dose	3	1 2 3

Number of observations 15

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The GLM Procedure
Repeated Measures Analysis of Variance

Repeated Measures Level Information

Dependent Variable	week1	week3	week4	week5	week6	week7
Level of week	1	3	4	5	6	7

week_N represents the nth degree polynomial contrast for week

M Matrix Describing Transformed Variables

	week1	week3	week4
week_1	-.6900655593	-.2760262237	-.0690065559
week_2	0.5455447256	-.3273268354	-.4364357805
week_3	-.2331262021	0.6061281254	0.0932504808
week_4	0.0703659384	-.4817360399	0.5196253913
week_5	-.0149872662	0.2248089935	-.5994906493

week_N represents the nth degree polynomial contrast for week

M Matrix Describing Transformed Variables

	week5	week6	week7
week_1	0.1380131119	0.3450327797	0.5520524475
week_2	-.3273268354	0.0000000000	0.5455447256
week_3	-.4196271637	-.4662524041	0.4196271637
week_4	0.2760509891	-.6062296232	0.2219233442
week_5	0.6744269805	-.3596943896	0.0749363312

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The GLM Procedure
Repeated Measures Analysis of Variance
Tests of Hypotheses for Between Subjects Effects

Source	DF	Type III SS	Mean Square	F Value	Pr > F
dose	2	18548.0667	9274.0333	1.06	0.3782
Error	12	105434.2000	8786.1833		

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The GLM Procedure
Repeated Measures Analysis of Variance
Univariate Tests of Hypotheses for Within Subject Effects

Source	DF	Type III SS	Mean Square	F Value	Pr > F
week	5	142554.5000	28510.9000	52.55	<.0001
week*dose	10	9762.7333	976.2733	1.80	0.0801
Error(week)	60	32552.6000	542.5433		

Source	Adj Pr > F G - G	H - F
week	<.0001	<.0001
week*dose	0.1457	0.1103
Error(week)		

Greenhouse-Geisser Epsilon	0.4856
Huynh-Feldt Epsilon	0.7191

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The GLM Procedure
Repeated Measures Analysis of Variance
Analysis of Variance of Contrast Variables

week_N represents the nth degree polynomial contrast for week

Contrast Variable: week_1

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Mean	1	131764.8029	131764.8029	87.35	<.0001
dose	2	2495.2133	1247.6067	0.83	0.4608
Error	12	18100.8743	1508.4062		

Contrast Variable: week_2

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Mean	1	2011.479365	2011.479365	6.67	0.0240
dose	2	4489.677778	2244.838889	7.45	0.0079
Error	12	3617.509524	301.459127		

Contrast Variable: week_3

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Mean	1	2862.193623	2862.193623	9.19	0.0104
dose	2	694.109855	347.054928	1.11	0.3597
Error	12	3736.192174	311.349348		

Contrast Variable: week_4

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Mean	1	3954.881058	3954.881058	17.28	0.0013
dose	2	1878.363604	939.181802	4.10	0.0439
Error	12	2746.984214	228.915351		

Contrast Variable: week_5

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Mean	1	1961.143097	1961.143097	5.41	0.0384
dose	2	205.368763	102.684382	0.28	0.7583
Error	12	4351.039802	362.586650		

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The GLM Procedure

Class Level Information

Class	Levels	Values
dose	3	1 2 3

Number of observations 15

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The GLM Procedure
Repeated Measures Analysis of Variance

Repeated Measures Level Information

Dependent Variable	week1	week3	week4	week5	week6	week7
Level of week	1	3	4	5	6	7

week_N represents the nth successive difference in week

M Matrix Describing Transformed Variables

	week1	week3	week4
week_1	1.000000000	-1.000000000	0.000000000
week_2	0.000000000	1.000000000	-1.000000000
week_3	0.000000000	0.000000000	1.000000000
week_4	0.000000000	0.000000000	0.000000000
week_5	0.000000000	0.000000000	0.000000000

week_N represents the nth successive difference in week

M Matrix Describing Transformed Variables

	week5	week6	week7
week_1	0.000000000	0.000000000	0.000000000
week_2	0.000000000	0.000000000	0.000000000

```
week_3      -1.000000000       0.000000000       0.000000000
week_4       1.000000000      -1.000000000       0.000000000
week_5       0.000000000       1.000000000      -1.000000000
```

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The GLM Procedure
Repeated Measures Analysis of Variance
Tests of Hypotheses for Between Subjects Effects

Source	DF	Type III SS	Mean Square	F Value	Pr > F
dose	2	18548.0667	9274.0333	1.06	0.3782
Error	12	105434.2000	8786.1833		

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The GLM Procedure
Repeated Measures Analysis of Variance
Univariate Tests of Hypotheses for Within Subject Effects

Source	DF	Type III SS	Mean Square	F Value	Pr > F
week	5	142554.5000	28510.9000	52.55	<.0001
week*dose	10	9762.7333	976.2733	1.80	0.0801
Error(week)	60	32552.6000	542.5433		

Source	Adj Pr > F G - G	Adj Pr > F H - F
week	<.0001	<.0001
week*dose	0.1457	0.1103
Error(week)		

Greenhouse-Geisser Epsilon	0.4856
Huynh-Feldt Epsilon	0.7191

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The GLM Procedure
Repeated Measures Analysis of Variance
Analysis of Variance of Contrast Variables

week_N represents the nth successive difference in week

Contrast Variable: week_1

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Mean	1	35721.60000	35721.60000	50.00	<.0001
dose	2	1112.40000	556.20000	0.78	0.4810
Error	12	8574.00000	714.50000		

Contrast Variable: week_2

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Mean	1	23128.06667	23128.06667	77.59	<.0001
dose	2	1980.13333	990.06667	3.32	0.0711
Error	12	3576.80000	298.06667		

Contrast Variable: week_3

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Mean	1	836.266667	836.266667	1.30	0.2772
dose	2	2.133333	1.066667	0.00	0.9983
Error	12	7743.600000	645.300000		

Contrast Variable: week_4

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Mean	1	2331.26667	2331.26667	2.10	0.1734
dose	2	6618.53333	3309.26667	2.97	0.0893
Error	12	13351.20000	1112.60000		

Contrast Variable: week_5

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Mean	1	17136.60000	17136.60000	27.69	0.0002
dose	2	619.20000	309.60000	0.50	0.6184
Error	12	7425.20000	618.76667		

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The GLM Procedure

Class Level Information

Class	Levels	Values
dose	3	1 2 3

Number of observations 15

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The GLM Procedure
Repeated Measures Analysis of Variance

Repeated Measures Level Information

Dependent Variable	week1	week3	week4	week5	week6	week7
Level of week	1	2	3	4	5	6

week_N represents the contrast between the nth level of week and the mean of subsequent levels

M Matrix Describing Transformed Variables

	week1	week3	week4
week_1	1.000000000	-0.200000000	-0.200000000
week_2	0.000000000	1.000000000	-0.250000000
week_3	0.000000000	0.000000000	1.000000000
week_4	0.000000000	0.000000000	0.000000000
week_5	0.000000000	0.000000000	0.000000000

week_N represents the contrast between the nth level of week and the mean of subsequent levels

M Matrix Describing Transformed Variables

	week5	week6	week7
week_1	-0.200000000	-0.200000000	-0.200000000
week_2	-0.250000000	-0.250000000	-0.250000000
week_3	-0.333333333	-0.333333333	-0.333333333
week_4	1.000000000	-0.500000000	-0.500000000
week_5	0.000000000	1.000000000	-1.000000000

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The GLM Procedure
Repeated Measures Analysis of Variance
Tests of Hypotheses for Between Subjects Effects

Source	DF	Type III SS	Mean Square	F Value	Pr > F
dose	2	18548.0667	9274.0333	1.06	0.3782
Error	12	105434.2000	8786.1833		

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The GLM Procedure
Repeated Measures Analysis of Variance
Univariate Tests of Hypotheses for Within Subject Effects

Source	DF	Type III SS	Mean Square	F Value	Pr > F
week	5	142554.5000	28510.9000	52.55	<.0001
week*dose	10	9762.7333	976.2733	1.80	0.0801
Error(week)	60	32552.6000	542.5433		

Source	Adj Pr > F G - G	H - F
week	<.0001	<.0001
week*dose	0.1457	0.1103
Error(week)		

Greenhouse-Geisser Epsilon 0.4856
Huynh-Feldt Epsilon 0.7191

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The GLM Procedure
Repeated Measures Analysis of Variance
Analysis of Variance of Contrast Variables

week_N represents the contrast between the nth level of week and the mean of subsequent levels

Contrast Variable: week_1

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Mean	1	114791.2560	114791.2560	93.69	<.0001
dose	2	343.6960	171.8480	0.14	0.8705
Error	12	14701.9680	1225.1640		

Contrast Variable: week_2

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Mean	1	35065.83750	35065.83750	64.01	<.0001
dose	2	481.90000	240.95000	0.44	0.6541
Error	12	6574.32500	547.86042		

Contrast Variable: week_3

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Mean	1	2200.185185	2200.185185	3.10	0.1037
dose	2	3888.059259	1944.029630	2.74	0.1046
Error	12	8512.755556	709.396296		

Contrast Variable: week_4

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Mean	1	12936.01667	12936.01667	20.93	0.0006
dose	2	8797.73333	4398.86667	7.12	0.0092
Error	12	7416.50000	618.04167		

Contrast Variable: week_5

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Mean	1	17136.60000	17136.60000	27.69	0.0002
dose	2	619.20000	309.60000	0.50	0.6184
Error	12	7425.20000	618.76667		