Chapter 6

Repeated measures data

6.1 Models for repeated measures

When measurements are repeated on the same subjects, for example students or animals, a 2-level hierarchy is established with measurement repetitions or occasions as level 1 units and subjects as level 2 units. Such data are often referred to as ‘longitudinal’ as opposed to ‘cross-sectional’ where each subject is measured only once. Thus, we may have repeated measures of body weight on growing animals or children, repeated test scores on students or repeated interviews with survey respondents. It is important to distinguish two classes of models which use repeated measurements on the same subjects. In one, earlier measurements are treated as covariates rather than responses. This was done for the educational data analysed in chapters 2 and 3, and will often be more appropriate when there are a small number of discrete occasions and where different measures are used at each one. In the other, usually referred to as ‘repeated measures’ models, all the measurements are treated as responses, and it is this class of models we shall discuss here. A detailed description of the distinction between the former 'conditional' models and the latter 'unconditional' models can be found in Goldstein (1979) and Plewis (1985).

We may also have repetition at higher levels of a data hierarchy. For example, we may have annual examination data on successive cohorts of 16-year-old students in a sample of schools. In this case the school is the level 3 unit, year is the level 2 unit and student the level 1 unit. We may even have a combination of repetitions at different levels: in the previous example, with the students themselves being measured on successive occasions during the years when they take their examination. We shall also look at an example where there are responses at both level 1 and level 2, that is specific to the occasion and to the subject. It is worth pointing out that in repeated measures models typically most of the variation is at level 2, so that the proper specification of a multilevel model for the data is of particular importance.

The link with the multivariate data models of chapter 4 is also apparent where the occasions are fixed. For example, we may have measurements on the height of a sample of children at ages 11.0, 12.0, 13.0 and 14.0 years. We can regard this as having a multivariate response vector of 4 responses for each child, and perform an equivalent analysis, for example relating the measurements to a polynomial function of age. This multivariate approach has traditionally been used with repeated measures data (Grizzle and Allen, 1969). It cannot, however, deal with data with an arbitrary spacing or number of occasions and we shall not consider it further.

In all the models considered so far we have assumed that the level 1 residuals are uncorrelated. For some kinds of repeated measures data, however, this assumption will not be reasonable, and we shall investigate models which allow a serial correlation structure for these residuals.

We deal only with continuous response variables in this chapter. We shall discuss repeated measures models for discrete response data in chapter 7.

6.2 A 2-level repeated measures model

Consider a data set consisting of repeated measurements of the heights of a random sample of children. We can write a simple model

$$y_{ij} = b_{0j} + b_{1j} x_{ij} + e_{ij} \qquad (6.1)$$

This model assumes that height (Y) is linearly related to age (X) with each subject having their own intercept and slope so that

$$E(b_{0j}) = b_0, \quad E(b_{1j}) = b_1$$

$$\mathrm{var}(b_{0j}) = s^2_{u0}, \quad \mathrm{var}(b_{1j}) = s^2_{u1}, \quad \mathrm{cov}(b_{0j}, b_{1j}) = s_{u01}, \quad \mathrm{var}(e_{ij}) = s^2_e$$

There is no restriction on the number or spacing of ages, so that we can fit a single model to subjects who may have one or several measurements. We can clearly extend (6.1) to include further explanatory variables, measured either at the occasion level, such as time of year or state of health, or at the subject level such as birthweight or gender. We can also extend the basic linear function in (6.1) to include higher order terms and we can further model the level 1 residual so that the level 1 variance is a function of age.

We explored briefly a nonlinear model for growth measurements in chapter 5. Such models have an important role in certain kinds of growth modelling, especially where growth approaches an asymptote as in the approach to adult status in animals. In the following sections we shall explore the use of polynomial models which have a more general applicability and for many applications are more flexible (see Goldstein, 1979 for a further discussion). We introduce examples of increasing complexity, and including some nonlinear models for level 1 variation using the results of chapter 5.

6.3 A polynomial model example for adolescent growth and the prediction of adult height

Our first example combines the basic 2-level repeated measures model with a multivariate model to show how a general growth prediction model can be constructed. The data consist of 436 measurements of the heights of 110 boys between the ages of 11 and 16 years together with measurements of their height as adults and estimates of their bone ages at each height measurement based upon wrist radiographs. A detailed description can be found in Goldstein (1989b). We first write down the three basic components of the model, starting with a simple repeated measures model for height using a 5-th degree polynomial.

$$y^{(1)}_{ij} = \sum_{h=0}^{5} b^{(1)}_h x^h_{ij} + \sum_{h=0}^{2} u^{(1)}_{hj} x^h_{ij} + e^{(1)}_{ij} \qquad (6.2)$$

where the level 1 term e_{ij} may have a complex structure, for example a decreasing variance with increasing age.

The measure of bone age is already standardised since the average bone age for boys of a given chronological age is equal to this age for the population. Thus we model bone age using an overall constant to detect any average departure for this group together with between-individual and within-individual variation.

$$y^{(2)}_{ij} = b^{(2)}_0 + \sum_{h=0}^{1} u^{(2)}_{hj} x^h_{ij} + e^{(2)}_{ij} \qquad (6.3)$$

For adult height we have a simple model with an overall mean and level 2 variation. If we had more than one adult measurement on individuals we would be able to estimate also the level 1 variation among adult height measurements; in effect measurement errors.

$$y^{(3)}_j = b^{(3)}_0 + u^{(3)}_{0j} \qquad (6.4)$$

We now combine these into a single model using the following indicators

$d_{ij}^{(1)} = 1, \quad \textit{if growth period measurement}, \quad 0 \textit{ otherwise}$

$d_{ij}^{(2)} = 1, \quad \textit{if bone age measurement}, \quad 0 \textit{ otherwise}$

$d_{j}^{(3)} = 1, \quad \textit{if adult height measurement}, \quad 0 \textit{ otherwise}$

$$y_{ij} = d_{ij}^{(1)} \left(\sum_{h=0}^{5} b_h^{(1)} x_{ij}^h + \sum_{h=0}^{2} u_{hj}^{(1)} x_{ij}^h + e_{ij}^{(1)} \right) + d_{ij}^{(2)} \left(b_0^{(2)} + \sum_{h=0}^{1} u_{hj}^{(2)} x_{ij}^h + e_{ij}^{(2)} \right) + d_j^{(3)} \left(b_0^{(3)} + u_{0j}^{(3)} \right) \qquad (6.5)$$

At level 1 the simplest model, which we shall assume, is that the residuals for bone age and height are independent, although dependencies could be created, for example if the model was incorrectly specified at level 2. Thus, level 1 variation is specified in terms of two variance terms. Although the model is strictly a multivariate model, because the level 1 random variables are independent it is unnecessary to specify a 'dummy' level 1 with no random variation as in chapter 4. If, however, we allow correlation between height and bone age then we will need to specify the model with no variation at level 1, the variances and covariance between bone age and height at level 2 and the between-individual variation at level 3.

Table 6.1 shows the fixed and random parameters for this model, omitting the estimates for the between-individual variation in the quadratic and cubic coefficients of the polynomial growth curve. We see that there is a large correlation between adult height and height and small correlations between the adult height and the height growth and the bone age coefficients. This implies that the height and bone age measurements can be used to make predictions of adult height. In fact these predicted values are simply the estimated residuals for adult height. For a new individual, with information available at one or more ages on height or bone age, we simply estimate the adult height residual using the model parameters. Table 6.2 shows the estimated standard errors associated with predictions made on the basis of varying amounts of information. It is clear that the main gain in efficiency comes with the use of height with a smaller gain from the addition of bone age.

Table 6.1 Height (cm) for adolescent growth, bone age, and adult height for a sample of boys.
Age measured about 13.0 years. Level 2 variances and covariances shown; correlations in brackets.

Parameter	Estimate (s.e.)
Fixed	
Adult Height	
Intercept	174.4
Group (A-B)	0.25 (0.50)
Height:	
Intercept	153.0
Age	6.91 (0.20)
Age^2	0.43 (0.09)
Age^3	-0.14 (0.03)
Age^4	-0.03 (0.01)
Age^5	0.03 (0.03)
Bone Age:	
Intercept	0.21 (0.09)
Age	0.03 (0.03)

Random
Level 2

	Adult Height	Height intercept	Age	Bone Age Intcpt.
Adult Height	62.5			
Height intercept	49.5 (0.85)	54.5		
Age	1.11 (0.09)	1.14 (0.09)	2.5	
Bone Age Intcpt.	0.57 (0.08)	3.00 (0.44)	0.02 (0.01)	0.85

Level 1 variance	
Height	0.89
Bone age	0.18

The method can be used for any measurements, either to be predicted or as predictors. In particular, covariates such as family size or social background can be included to improve the prediction. We can also predict other events of interest, such as the estimated age at maximum growth velocity.

Fig 6.2 Standard errors for height predictions for specified combinations of height and bone age measurements.

		Height measures (age)		
		None	11.0	11.0 12.0
Bone age measures				
None			4.3	4..2
11.0		7.9	3.9	3.8
11.0	12.0	7.9	3.7	3.7

6.4 Modelling an autocorrelation structure at level 1.

So far we have assumed that the level 1 residuals are independent. In many situations, however, such an assumption would be false. For growth measurements the specification of level 2 variation serves to model a separate curve for each individual, but the between-individual variation will typically involve only a few parameters, as in the previous example. Thus if measurements on an individual are obtained very close together in time, they will tend to have similar departures from that individual's underlying growth curve. That is, there will be 'autocorrelation' between the level 1 residuals. Examples arise from other areas, such as economics, where measurements on each unit, for example an enterprise or economic system, exhibit an autocorrelation structure and where the parameters of the separate time series vary across units at level 2.

A detailed discussion of multilevel time series models is given by Goldstein et al (1994). They discuss both the discrete time case, where the measurements are made at the same set of equal intervals for all level 2 units, and the continuous time case where the time intervals can vary. We shall develop the continuous time model here since it is both more general and flexible.

To simplify the presentation, we shall drop the level 1 and 2 subscripts and write a general model for the level 1 residuals as follows

$$\mathrm{cov}(e_t e_{t-s}) = s_e^2 f(s) \qquad (6.6)$$

Thus, the covariance between two measurements depends on the time difference between the measurements. The function $f(s)$ is conveniently described by a negative exponential reflecting the common assumption that with increasing time difference the covariance tends to a fixed value, $a s_e^2$, and typically this is assumed to be zero

$$f(s) = a + \exp(-g(b, z, s)) \qquad (6.7)$$

where b is a vector of parameters for explanatory variables z. Some choices for g are given in Table 6.3.

We can apply the methods described in Appendix 5.1 to obtain maximum likelihood estimates for these models, by writing the expansion

$$f(s, b, z) = \{1 + \sum_k b_{k,t} z_k g(H_t)\} f(H_t) - \sum_k b_{k,t+1} z_k g(H_t) f(H_t) \qquad (6.8)$$

so that the model for the random parameters is linear. Full details are given by Goldstein et al (1994).

6.5 A growth model with autocorrelated residuals

The data for this example consist of a sample of 26 boys each measured on nine occasions between the ages of 11 and 14 years (Harrison and Brush, (1990). The measurements were taken approximately 3 months apart. Table 6.4 shows the estimates from a model which assumes independent level 1 residuals with a constant variance. The model also includes a cosine term to model the seasonal variation in growth with time measured from the beginning of the year. If the seasonal component has amplitude a and phase g we can write

$$a\cos(t + g) = a_1 \cos(t) - a_2 \sin(t)$$

In the present case the second coefficient is estimated to be very close to zero and is set to zero in the following model. This component results in an average growth difference between summer and winter estimated to be about 0.5 cm.

We now fit in table 6.5 the model with $g = b_0 s$ which is the continuous time version of the first order autoregressive model.

The fixed part and level 2 estimates are little changed. The autocorrelation parameter implies that the correlation between residuals 3 months (0.25 years) apart is 0.19.

Table 6.3 Some choices for the covariance function g for level 1 residuals.

$g = b_0 s$	For equal intervals this is a first order autoregressive series.
$g = b_0 s + b_1(t_1 + t_2) + b_2(t_1^2 + t_2^2)$	For time points t_1, t_2 this implies that the variance is a quadratic function of time.
$g = \begin{cases} b_0 s \text{ if no replicate} \\ b_1 \text{ if replicate} \end{cases}$	For replicated measurements this gives an estimate of measurement reliability $\exp(-b_1)$.
$g = (b_0 + b_1 z_{1j} + b_2 z_{2ij})s$	The covariance is allowed to depend on an individual level characteristic (e.g. gender) and a time-varying characteristic (e.g. season of the year or age).
$g = \begin{cases} b_0 s + b_1 s^{-1}, \quad s > 0 \\ 0, \quad s = 0 \end{cases}$	Allows a flexible functional form, where the time intervals are not close to zero.

Table 6.4 Height as a fourth degree polynomial on age, measured about 13.0 years. Standard errors in brackets; correlations in brackets for covariance terms.

Parameter	Estimate (s.e.)		
Fixed			
Intercept	148.9		
age	6.19 (0.35)		
age^2	2.17 (0.46)		
age^3	0.39 (0.16)		
age^4	-1.55 (0.44)		
cos (time)	-0.24 (0.07)		
Random			
level 2			
	Intercept	age	age^2
Intercept	61.6 (17.1)		
age	8.0 (0.61)	2.8 (0.7)	
age^2	1.4 (0.22)	0.9 (0.67)	0.7 (0.2)
level 1			
s_e^2	0.20 (0.02)		

Table 6.5 Height as a fourth degree polynomial on age, measured about 13.0 years. Standard errors in brackets; correlations in brackets for covariance terms. Autocorrelation structure fitted for level 1 residuals.

Parameter	Estimate (s.e.)		
Fixed			
Intercept	148.9		
age	6.19 (0.35)		
age^2	2.16 (0.45)		
age^3	0.39 (0.17)		
age^4	-1.55 (0.43)		
cos (time)	-0.24 (0.07)		
Random			
level 2			
	Intercept	age	age^2
Intercept	61.5 (17.1)		
age	7.9 (0.61)	2.7 (0.7)	
age^2	1.5 (0.25)	0.9 (0.68)	0.6 (0.2)
level 1			
s_e^2	0.23 (0.04)		
b	6.90 (2.07)		

6.6 Multivariate repeated measures models

We have already discussed the bivariate repeated measures model where the level 1 residuals for the two responses are independent. In the general multivariate case where correlations at level 1 are allowed, we can fit a full multivariate model by adding a further lowest level as described in chapter 4. For the autocorrelation model this will involve extending the models to include cross correlations. For example for two response variables with the model of table 6.5 we would write

$$\gamma = \sigma_{e1}\sigma_{e2}\exp(-\beta_{12}s)$$

The special case of a repeated measures model where some or all occasions are fixed is of interest. We have already dealt with one example of this where adult height is treated separately form the other growth measurements. The same approach could be used with, for example, birthweight or length at birth. In some studies, all individuals may be measured at the same initial occasion and we can choose to treat this as a covariate rather than as a response. This might be appropriate where individuals were divided into groups for different treatments following initial measurements.

6.7 Scaling across time

For some kinds of data, for example educational achievement scores, different measurements may be taken over time on the same individuals so that some form of standardisation may be needed before they can be modelled using the methods of this chapter. It is common in such cases to standardise the measurements so that at each measuring occasion they have the same population distribution. If this is done then we should not expect any trend in either the mean or variance over time, although there will still, in general, be between-individual variation. An alternative standardisation procedure is to convert scores to age equivalents; that is to assign to each score the age for which that score is the population mean or median. Where scores change smoothly with age this has the attraction of providing a readily interpretable scale. Plewis (1993) uses a variant of this in which the coefficient of variation at each age is also fixed to a constant value. In general, different standardisations may be expected to lead to different inferences. The choice of standardisation is in effect a choice about the appropriate scale along which measurements can be equated so that any interpretation needs to recognise this. A further discussion of this issue is given by Plewis (1994).

6.8 Cross-over designs

A common procedure for comparing the effects of two different treatments A, B, is to divide the sample of subjects randomly into two groups and then to assign A to one group followed by B and B to the other group followed by A. The potential advantage of such a design is that the between-individual variation can be removed from the treatment comparison. A basic model for such a design with two treatments, repeated measurements on individuals and a single group effect can be written as follows

$$y_{ij} = \beta_0 + \beta_1 x_{1ij} + \beta_2 x_{2ij} + u_{0j} + u_{2j}x_{2ij} + e_{ij} \qquad (6.9)$$

where X_1 is a dummy variable for time period and X_2 is a dummy variable for treatment. In this model we have not modelled the responses as a function of time within treatment, but this can be added in the standard fashion described in previous sections. In the random part at level 2 we allow between-individual variation for the treatment difference and we can also structure the level 1 variance to include autocorrelation or different variances for each treatment or time period.

One of the problems with such designs is so called ‘carry over’ effects whereby exposure to an initial treatment leaves some individuals more or less likely to respond positively to the second treatment. In other words, the u_{2j} may depend on the order in which the treatments were applied. To model this we can add an additional term to the random part of the model, say $u_{3j}d_{3ij}$, where d_{3ij} is a dummy variable which is 1 when A precedes B and the second treatment is being applied and zero otherwise. This will also have the effect of allowing level 2 variances to depend on the ordering of treatments. The extension to more than two treatment periods and more than two treatments is straightforward.