Repeated Measurement Models: A Survey

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Abstract

The demand for models of repeated measurements has known a phenomenal growth in recent years, as applications are found in all areas of scientific endeavour. In this review, similarities in the approaches to modelling different kinds of response variables, normal, discrete, and duration, are emphasized. Any appropriate model should take into account two possible types of stochastic dependence, random variability or heterogeneity among units in the population and, in longitudinal studies, stochastic time dependence among responses. Finally, a number of problem areas for further research are outlined.

KEYWORDS: autoregression, conjugate distribution, counting process, dependence, discrete data, duration data, exponential dispersion model, exponential family, growth curve, longitudinal study, Markov process, multivariate distribution, overdispersion, random effects.

1 Introduction

Repeated measurements, as the name suggests, are observations of the same characteristic which are made several times (but not necessarily separated in time!). What distinguishes such observations from those in more traditional statistical data modelling is that

- the same variable is measured on the same observational unit more than once: the responses are not independent as in the usual regression analysis and
- more than one observational unit is involved: the responses do not form a simple time series.

Thus, one special characteristic of repeated measurements is that more than one observation on the *same* response variable is available on each observational unit. For a set of responses on each of several units, those on the same one may often, but not always, be expected to be more closely related than those

among different ones. Thus, we are in a situation of stochastically dependent data which must be modelled by some form of multivariate methods. This may be distinguished from more general multivariate methods which treat interdependence among *different* types of response variables.

Repeated measurement of the same variable on the same unit may be necessary for a number of reasons.

- Repeated observation may be the only way of obtaining the required measurement, as in counting the occurrences of some phenomenon.
- Interest may centre on the evolution of some response, given initial conditions which may or may not be fixed experimentally. Simple growth curves are the most common example.
- The investigator may wish to compare the effects of continued administration of some treatment over time.
- Different treatments may need to be compared in a situation where variability among units is an important uncontrollable factor. To increase precision, intra-unit comparisons of the different treatments are necessary.
- One may want to study the total effects of different sequences of treatments, as in the study of crop rotations in agriculture.

In recent years, the literature on repeated measures has reached explosive proportions. Lindsey (1993) provides a bibliography over over 1300 items to the end of 1992, and this is far from complete. Here, only a few of the more important highlights can be touched upon. Emphasis will be placed on the use of similar models for different types of response variables.

2 Types of responses

In the statistical literature, the most common models for repeated responses assume them to be continuous measurements taking any real value. Such models are most commonly based on some variation of the *multivariate normal distribution*. Much of the original work on repeated measurements evolved around this type of response, as developments and special cases of the Potthoff and Roy (1964) growth model,

$$\mathrm{E}[\mathbf{Y}] = \mathbf{XBZ}$$

where $\mathbf{Y}$ and $\mathbf{X}$ are the response and design matrices, while $\mathbf{B}$ is a $C \times P$ location parameter matrix and $\mathbf{Z}$ is a $P \times R$ matrix of covariates changing with the responses on a unit, most often simply a polynomial over the R points in time. In this general multivariate model, the variance-covariance matrix, $\mathbf{\Sigma}$, is assumed to have an unstructured form. Most subsequent developments have concentrated

on more complete specifications of this matrix (Diggle, 1988; Elston and Grizzle, 1962; Jones and Ackerson, 1990; Laird and Ware, 1982), although some work has been done on nonlinear models for the location parameters (Berkey, 1982; Frey, 1992; Gennings, Chinchilli, and Carter, 1989; Palmer, Phillips, and Smith, 1991; Vonesh and Carter, 1992), and occasionally both simultaneously (Heitjan, 1991a, b).

However, *categorical* and *count data* play very important roles in scientific observation. For example, they are the principal type of response in *panel studies*. Counts are always repeated event data, where nothing distinguishes the events on a unit, so that they are aggregated as the count. On the other hand, categorical data are only repeated observations of events if they occur to the same unit, but are not aggregated because treatments or covariates distinguish among them. However, such events may be aggregated as frequencies across units having exactly the same profiles of explanatory variables. The difference, from our perspective, is that, for a count, the response of interest is the frequency of occurrence of one or more events, necessarily on the same unit, while, for categorical data, the response is an indicator of which of a number of events has occurred. Categorical data are only repeated measurements if observed several times on the same unit.

All of the well-known work on *overdispersion* (Anderson, 1988; Ashby *et al.*, 1992; Breslow, 1984; Cox, 1983; Crowder, 1978; Gouriéroux, Montfort, and Trognon, 1984; Hausman, Hall, and Griliches, 1984; Heckman and Willis, 1977; Lawless, 1987; Mosimann, 1962; Prentice, 1986; Williams, 1982) and *Markov chains* (Anderson and Goodman, 1957; Billingsley, 1961; Chatfield, 1973; Cox, 1955, 1958; Lawless, and McLeish, 1984; Muenz, and Rubinstein, 1985; Spilerman, 1972; Zeger, Liang, and Self, 1985) is relevant here.

Another important area of scientific study involves the observation of *durations*, and, more generally, of *positive-valued responses*. These usually will have skewed marginals for which a normal distribution is not suitable. The classical solution of data transformations is unsatisfactory, because it provides no information about the underlying data generating mechanism. The special case of durations is even more complex.

If we measure survival in living beings, there can be no repetition, because death occurs at the end. On the other hand, consider the classical measurement of periods between successive breakdowns of a machine or the succession of periods of unemployment or of illness of individuals. This is often known as an *event* or *life history* study; many of the most important developments have come in the social sciences (Blossfeld, Hamerle, and Mayer, 1989; Hannan, and Carroll, 1981; Heckman, 1978; Heckman and Borjas, 1980; Heckman and Singer, 1985; Lancaster, 1990: Tuma, 1976; Tuma, Hannan, and Groeneveld, 1976), more recently penetrating into the more biological fields (Aalen *et al.*, 1980; Andersen and Borgan, 1985; Clayton, 1988).

A close relationship exists between durations and counts in longitudinal event history data. This is clear in the *counting process* approach to dura-

tion data, where the number of events is accumulated over a period of time, thus uniting a duration and a count.

Event history data are peculiar in that the response, whether taken as elapsed duration between events or cumulated counts of events, is a direct function of time. This contrasts with many other longitudinally observed repeated responses, which are simply attributes of the unit, such as blood pressure, measured at various points in time. They will have an evolution, but not necessarily accumulation. Intermediate are the 'growth' type responses, which have a predominant tendency, either to become larger or smaller, usually up to some asymptotic limit, but where successive differences are not necessarily in the same direction: a growing rat may lose weight over one observation period, but events cannot disappear after they have occurred.

3 Heterogeneity

The units which are observed for repeated measures will usually be inherently heterogeneous. Some will systematically respond more strongly than others. In medical studies, such as survival analysis, this is known as *frailty*. In studies of counts of accidents, it is called *proneness*. In both cases, the rate at which events is occurring is varying in some unknown way across the observation units. Explanatory variables, which might explain these differences, are not available, and may not be of interest in the study at hand. In other words, the variability of responses on a unit will often be smaller than that across units. If responses on a unit were independent, the covariability among them would be zero. In contrast, here, we shall require a *uniform* intra-class or intra-unit covariability model. All inter-relationships among responses within a unit are equal, but nonzero. In this way, we can model directly the stochastic dependence structure of our observations.

For count data, we find the overdispersion models mentioned above. For normally distributed data, we have variance components models. The variance-covariance matrix in the Potthoff and Roy model is constrained to have a constant off-diagonal covariance. Unfortunately, generalization to other models based on other types of responses is rarely easy. Generally, non-normal distributions require the specification of all higher order moments and these are often closely related to the mean or location parameter. Suitable multivariate distributions are not often available.

A second fruitful approach is to assume that some parameter describing the different reactions of the units is varying in a random way throughout the population. This is known as a *random effects model*. Suppose that the distribution of responses, given the parameter value, is $f(y|\lambda)$ and that the random distribution of the parameter is given by $p(\lambda;\gamma)$. Then, the marginal distribution of

the response can be obtained by integration:

$$f(y;\gamma) = \int f(y|\lambda)p(\lambda;\gamma)d\lambda$$

It turns out that, if both distributions are normal, the result is identical to the variance components model mentioned above.

One special case of particular interest is when $p(\lambda;\gamma)$ is the *conjugate distribution* to $f(y|\lambda)$, because then $f(y;\gamma)$ can be obtained in closed form. For the exponential family,

$$f(y|\boldsymbol{\lambda}) = \mathrm{e}^{\boldsymbol{\lambda}^T\mathbf{t}(y)-\kappa(\boldsymbol{\lambda})}$$

a conjugate distribution, also a member of the exponential family, always exists:

$$p(\boldsymbol{\lambda};\gamma_0,\boldsymbol{\gamma}) = \mathrm{e}^{\boldsymbol{\lambda}^T\boldsymbol{\gamma}-\gamma_0\kappa(\boldsymbol{\lambda})}$$

as it does for generalized linear models. The normal random effects model is one such case, but other well-known examples include the negative binomial distribution for counts and the beta-binomial distribution for overdispersed binomial data. If a conjugate distribution is not available or not suitable, numerical integration must usually be performed.

If the covariates are introduced into the conditional distribution, $f(y|\lambda)$,

$$g(\lambda_i) = \sum_k \beta_{ik}\, x_{ik}$$

where $g(\cdot)$ is a link function, we have a 'subject-specific' model. In this case, β_{i0} is usually taken as random. Here, the x_{ik} can distinguish among responses on a unit, as well as among units.

If the covariates are introduced after integration, into the marginal distribution, $f(y;\gamma)$,

$$g(\gamma_i) = \sum_k \beta_{ik}\, x_{ik}$$

we have a 'population-averaged' model. Obviously, in this latter case, covariates which distinguish among responses on a unit cannot be used; the x_{ik} must remain constant for all responses on a unit. This model provides an averaged measure of differences (in treatments, etc.) over responses among units. However, for normal models, the two are identical.

Various heterogeneity models have been suggested for categorical data (Ashby *et al.*, 1992; Koch *et al.*, 1977; Laird, 1991; Preisler, 1988) as well as for duration data (Clayton, 1978; Clayton and Cuzick, 1985; Heckman and Singer, 1984a, b; Hougaard, 1984, 1986a, b; Lancaster, 1990; Oakes, 1982, 1986, 1989). Particular care must be taken in the latter case. Usually, only a 'window' is

available on the event history. If the population is heterogeneous, events of the more frail or prone units will be over-represented (Blossfeld and Hamerle, 1992; Vaupel and Yashin, 1985).

An extension of the random effects model, in a regression situation, is to make a number of the regression coefficients random, a random coefficients model. This has been extensively studied in the normal case (Elston and Grizzle, 1962; Laird and Ware, 1982),

$$\mathrm{E}[\mathbf{Y}|\mathbf{\Lambda}] = \mathbf{XBZ} + \mathbf{\Lambda V} \qquad \Lambda \sim \mathrm{MVN}(\mathbf{0}, \mathbf{I} \otimes \mathbf{\Delta})$$

where $\mathbf{Z}$ and $\mathbf{V}$ are polynomials in time, so that the model can be used to induce complex structures in the variance-covariance matrix. However, the actual meaning of such coefficients is usually difficult to interpret. They are also difficult to extend to the nonlinear and nonnormal cases, so that they should be avoided unless there is solid scientific reasons for using them.

Because of the difficulties in directly constructing models of covariability among responses for non-normal data, certain non-model based procedures, called *generalized estimating equations*, have been put forward (Gilmour, Anderson, and Rae, 1985; Liang and Zeger, 1986). These are based on the estimating equations for univariate generalized linear models, into which a variance-covariance is artificially inserted,

$$\sum_{i=1}^{N} \mathbf{Z}_i \mathrm{diag}\left[\frac{\partial \mu_{ik}}{\partial \eta_{ik}}\right] [\mathbf{U}_i^{\frac{1}{2}} \mathbf{R}_i \mathbf{U}_i^{\frac{1}{2}}]^{-1} \mathbf{d}_i = 0$$

where $\mathbf{Z}_i$ is the $P \times R$ design matrix for the unit, $\mathbf{d}_i = \mathbf{y}_i - \boldsymbol{\mu}_i$ a $R \times 1$ vector, and η the linear regression structure, with $\mathbf{R}$ some correlation matrix and $\mathbf{U}_i = \mathrm{diag}(\mathrm{var}[Y_{ik}])$. The result is that the relation of the estimating equations to a likelihood function, and to a probability-based model, is usually destroyed. Besides the difficulty in interpreting the results of such an approach, it has the additional handicap that inferences can only be performed using the notoriously poorly performing asymptotic standard errors of the parameter estimates (Wald tests).

Heterogeneity is a general problem in repeated measurements data. If the responses on a unit are recorded more or less simultaneously, as, for example, in family and litter studies, agricultural split plots, or similar organs in the same body, this will be the only type of stochastic dependence which must be modelled.

4 Longitudinal data

Many repeated measurement studies involved collection of data on units over time. Even survival studies necessitate continuous observation over time, although only one final event is being recorded. When time is involved, a second

kind of stochastic dependence among observations on a unit will usually be present: observations closer together in time will often be more closely related. Because the series on any given unit will usually be fairly short, a first order Markov model will usually be adequate. Note, however, that, in such short periods, the series will often be nonstationary.

For normally distributed data, *autoregression models* will usually be suitable. As for heterogeneity, a identical models can be obtained by directly modelling the variance-covariance matrix or by conditioning on lagged variables. Some fairly complex models have been developed in this domain, combining random effects with autoregression (Diggle, 1988; Heitjan, 1991a, b; Jones and Ackerson, 1990).

Again, for non-normal data, it is usually difficult to model the stochastic dependence directly, so that conditioning must be used

$$g(\mu_{ik}) = \rho y_{i,k-1} + \sum_k \beta_{ik} x_{ik}$$

For categorical data, *Markov chains* are easily handled as logistic or log linear models (Lindsey, 1992). Counts can also be handled by conditioning in log linear models. However, counts of events accumulated over time may be subject to *contagion*, a time dependence among events. As is well known, if only aggregated counts are available, this cannot be distinguished from the proneness of heterogeneous units. The two models can only be compared if the time spacing of the events is available. And, of course, both proneness and contagion may simultaneously be present.

The situation for event history data is more complex. In the simplest case, intervals are independent and identically distributed, so that we have a *renewal process* and all of the standard models of survival analysis can be applied. When there is time dependence, conditioning can be introduced to create *nonhomogeneous processes*. One simple and very useful model is the *birth process*, where conditioning is on the number of previous events, but one might also condition on the length of the previous period(s). Within a period, conditioning on time since the previous event is the same as replacing a Poisson process by a nonhomogeneous one, such as a Weibull, gamma, or extreme value process. If an event signals a change of state for the unit, we have a *semi-Markov* or *Markov renewal process*.

The situation becomes more difficult when there are time-varying covariates which can change within the interval. Then, the distributions of the intervals can no longer be directly modelled. Instead, we have to look at the intensity of the event process, making it depend on the covariates, as well as any appropriate information about previous events. This is the counting process approach, which can be modelled as a log linear model for the presence or absence of an event in each small observation period.

Because the correlation matrix, $\mathbf{R}$, can have any arbitrary form, generalized

estimating equations can also be used for longitudinal data, although the same reservations about their interpretation still hold.

It cannot be emphasized too much that, for all types of responses, both heterogeneity and time stochastic dependence should be considered. Both may not prove necessary in any single case, but their presence should not be excluded *a priori*. They provide valuable information, in addition to covariate effects, which the scientist always finds very useful. As well, neglecting one can induce spurious dependence of the other type. Even if the stochastic dependence is not of direct interest, ignoring it and assuming independence among repeated observations on a unit will make the effects of interest more significant than they really are. Such an independence model operates as if there were more information in the data than actually exists.

5 Prospects

Although a few suitable multivariate distributions are slowly being developed (Arnold and Strauss, 1991; Genest and MacKay, 1986a, b; Jørgensen, 1992; Marshall and Olkin, 1988), the area is lagging far behind the complex requirements of modelling repeated measures data. At present, conditioning, whether on random parameters or lagged responses, is the only realistic way to set up most reasonable non-normal models.

It is surprising how many problems of repeated measurements can be coerced into the generalized linear model context, or, even more generally, as exponential dispersion models (Jørgensen, 1987, 1992)

$$f(\mathbf{y};\boldsymbol{\theta},\sigma^2) = a(\sigma^2,\mathbf{y})\mathrm{e}^{[\mathbf{y}^T\boldsymbol{\theta}-\kappa(\boldsymbol{\theta})]/\sigma^2}$$

The latter provide the generalization of the independent and identically distributed increments models of Brownian motion and Poisson processes to more general processes, such as the Bernoulli, inverse Gaussian, and gamma (Jørgensen, 1992; Seshadri, 1988). They are one promising avenue for developing the multivariate models necessary for repeated measures, especially for nonstationary longitudinal data. Another avenue which should be investigated is the set of conditions under which the scalar dispersion parameter, σ^2, in these models, can be generalized to a vector or matrix. The bivariate exponential conditionals models of Arnold and Strauss (1991) are examples.

Linear location models, including polynomials, are, at best, simple approximations to reality, where evolution towards an asymptote is the usual situation. As mentioned, a rapidly increasing amount of work on nonlinear models, with random effects and autoregression, is being produced for normal responses. However, little is yet available for non-normal data. Models handle heterogeneity *or* time dependence, and rarely nonlinear regression. Much work needs to be done here.

In any data recording done over time, censoring, such as dropouts or withdrawals, and other types of missing observations, are a major problem. Fairly strong assumptions usually have to be made about the randomness of the 'missing mechanism'. Certain results, particularly using martingale stopping times, are now available from survival analysis, but these need to be further extended for repetitions. The problem of heterogeneity in event history data was noted above. But even in simpler cases, such as growth curves, the implications of some units having time to reach an asymptote and others not, has not been studied.

As well, observation may often not be possible at regular intervals on each unit. Then, continuous time models are required. These are available for normally distributed data (Heitjan, 1991a, b; Jones and Ackerson, 1990; Jones and Boadi-Boateng, 1991), but little work has yet been done in other contexts. For example, few models are available for unequally space categorical or count data.

When continuously changing covariates, or responses, are involved, strong assumptions have to be made about their values between observation points. The effects of such assumptions need to be investigated.

Virtually no statistical computer packages are available for such multivariate responses. What is required is the next generation of software to follow the GLIM modelling strategy. Stochastic dependence structures, for heterogeneity and time dependence, must be easily selectable for a variety of non-normal models, in combination with a simple syntax which extends the Wilkinson and Rogers (1973) notation to nonlinear location models. Extensions of the Kalman filter, which have already proven their worth in normal models (Jones and Ackerson, 1990), seem to be the most promising algorithm for estimation (West, Harrison, and Migon, 1985).

With the ready availability of rapidly increasing computing power, one obstacle to fitting such complex models has been removed. However, further study is needed for the choice of stable initial values in iterative routines, and of ways of monitoring convergence before such software will be acceptable for everyday statistical use.

At present, repeated measurements is an area where scientists are generating vast quantities of data while the statisticians are incapable of providing them with the suitable models which can be routinely applied.

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