Multivariate Analysis and Its Applications
IMS Lecture Notes – Monograph Series (1994) Volume 24

A QUASILINEAR REGRESSION MODEL FOR CROSS-OVER TRIALS

BY JIQIAN FANG, SHUYING YANG AND BYRON JONES

Beijing Medical University and University of Kent at Canterbury

A quasilinear regression model for the analysis of data from a two-period, two-treatment cross-over trial is proposed. In a way similar to Fang, Mao and Jones (1990), the response (or output) is modelled as a function of the inputs, i.e. treatments, periods and residual effects. The model is such that the output at any particular time depends on the history of the inputs up to and including that particular time. The parameters in the model account for the treatment effects, the period effects and the decay rate of the residual effects. The method of statistical inference used is based on the likelihood function and the analysis of variance. Computer simulations show that the parameters are estimated satisfactorily. Finally, the model is illustrated by fitting it to two real data sets.

1. Introduction. When comparing the efficacy of two treatments in a clinical trial the classical approach is based on the parallel group design. In this design the patients are randomly divided into two groups and every patient in the first group receives treatment A and every patient in the second group receives treatment B. A major disadvantage of such a design is that, as patients vary greatly in their initial disease state and their response to therapy, the test for a treatment difference lacks power. The loss of power results from comparing treatments using between-subject information. An alternative, more powerful design, is the cross-over trial which uses within-subject information to compare the treatments. In the cross-over trial the patients are randomly divided into two groups. Each patient in the first group receives treatment A for a given period of time, then 'crosses over' to receive treatment B for a further equal period of time. Each patient in the second group receives B first, then crosses over to A. In such a design each patient serves as his or her own control and as such is very appealing to clinicians and pharmacologists.

A potential disadvantage of the cross-over trial is that the effect of the first treatment a patient receives might still be retained by the patient when the second treatment is administered. If this is the case then the effect seen

AMS 1980 Subject Classifications: 62J10, 62J20.

Key words: Cross-over trial, cumulative residual effect, quasilinear model.

in the second period will be the sum of the immediate effect of the treatment given in the second period and the residual effect of the treatment given in the first period. Often, if ethical, a wash-out period is introduced between the two treatment periods in order that the residual (carry-over) effect of the first treatment can be removed before the second treatment is given. During the wash-out period no treatment or placebo may be given. If the wash-out period is long enough for the first treatment to be removed, then the cross-over trial is vastly superior to the parallel group trial. However, wash-out periods may not be ethical or practical and so the possibility of residual effects in the second period must be allowed for.

Up to now a number of statistical methods have been proposed for the analysis of data from the two-treatment cross-over trial. Jones & Kenward (1989, Chapter 2) review the topic and give numerous references. One of the first parametric approaches is due to Grizzle (1965). A non-parametric approach has been described by Koch (1975).

In Grizzle's approach a preliminary test of equality of the residual effects of the treatments has to be done prior to comparing the direct treatment effects. If the preliminary test rejects the null hypotheses of equal residual effects, then the data in the second period are discarded and the comparison of treatments is based on the first period data as in the parallel group trial. Another disadvantage of this approach is that no attempt is made to formally model the history of the residual effects. Here we take account of the fact that the output at time t may depend on the history of the inputs up to and including time t.

2. The Quasilinear Regression Model. The model consists of the following components:

(1) The instantaneous input, which is a function of time and denoted by $e(t)$, and which describes the history of the inputs. The subscripts 11, 12 on $e(t)$ denote the input functions for treatments A and B respectively, in group I, and the subscripts 21 and 22 denote the same for group II. A particular, simple example of $e(t)$ is

$$e_{11}(t) = e_{22}(t) = \begin{cases} 1, & \text{during period 1;} \\ 0, & \text{otherwise.} \end{cases}$$

$$e_{12}(t) = e_{21}(t) = \begin{cases} 1, & \text{during period 2;} \\ 0, & \text{otherwise.} \end{cases}$$

More general forms which allow $e(t)$ to cater for different dose levels of A and B are also possible.

(2) The decay function $g(t)$ is a function of time t, indicating the retained residual effect at time t due to one unit of input at time $t = 0$. It is

assumed that $g(t) > 0$, $g(0) = 1$ and $g(t_1) > g(t_2)$ if $t_1 < t_2$. The exponential form $g(t) = \exp(-\nu t)$ is recommended in the following, although other forms might also be considered depending on the specific context of the trial.

(3) The cumulative residual function $r(t)$ is the sum of the residual effects up to time t due to the whole history of the inputs up to time t, i.e. $r(t) = \int_0^t e(\tau).g(t-\tau)d\tau$.

4. The effective input function $X(t)$ consists of two parts, the instantaneous input $e(t)$ and the cumulative residual $r(t)$, i.e. $X(t) = r(t) + e(t)$.

(5) The output function $Y(t)$ measures the effects of all the inputs up to time t and is expressed as $Y_i(t) = \gamma_i + \beta(t) + \alpha_1 X_{i1}(t) + \alpha_2 X_{i2}(t) + \epsilon_i(t)$, where the subscript i denotes the ith subject, $i = 1, 2, \ldots, n$ and $n = n_1 + n_2$. For $i = 1, 2, \ldots, n$, γ_i is the effect of the ith subject, $\beta(t)$ is a function of time t which describes the time effect, independent of the subject effect. The function $\beta(t)$ is assumed to be monotonic with piecewise constants. The parameters α_1 and α_2 are the effects of treatments A and B respectively. The input functions $X_{i1}(t)$ and $X_{i2}(t)$ are the effective input functions for treatments A and B, respectively, for subject i, with ν_1 and ν_2 defining the decay functions, respectively. Finally, $\epsilon_i(t)$ is a random effect which is a function of t and has a distribution which does not dependon i and t.

3. Monte-Carlo Simulation and Examples. To evaluate how well the parameters in the quasilinear model are estimated, some simulation studies were carried out. For given values of the parameters, 8 pairs of groups I and II were simulated with $n_1 = n_2 = 50$. The differences between the estimates and their true values were not statistically significant. The model proposed here therefore appears to be quite satisfactory for use in practice with real data.

The analysis of two example data sets (Han Qinqin (1987) and Patel (1985), respectively) showed that our approach produces more information on the treatments than provided by traditional methods.

4. Discussion. The proposed model has wide application and can cater for any length of wash-out period. The model is derived from that of Fang et al. (1990). In that latter model the output is the time to occurrence of certain point events. The output here is a measurement at certain prespecified time points. The model can be extended to cater for cross-over trials with more than two treatment periods and also to cater for trials in which the pattern of input varies among the patients. The latter extension would be of use in occupational epidemiology.

REFERENCES

CHIANG, C. L. and CONFORTI, P. M. (1989). A survival model and estimation of time to tumor. *Mathematical Sciences*, **94**, No. 1, 1.

FANG, J. Q., MAO, J. H. and JONES, B. (1990). A quasilinear survival model and its applications in epidemiology. (Submitted to *J.Statistics in Medicine*).

GRIZZLE, J. E. (1965). The two-period change over design and its use in clinical trials. *Biometrics*, **21**, 467–480.

HAN QINQIN. (1987). *New Drug Clinic.* **6**, 65–67.

JONES , B. and KENWARD, M. G. (1989). *Design and Analysis of Cross-over Trials.* Chapman and Hall: London.

KOCH, G. G. (1972). The use of non-parametric methods in the statistical analysis of the two-period change-over design. *Biometrics*, **28**, 577–584.

PATEL, H. I. (1983). Use of baseline measurements in two-period crossover designs. *Commun. Statist. Theor. Meth.*, **12**, 2693–2712.

DEPARTMENT OF BIOMATHEMATICS AND BIOSTATISTICS
BEIJING MEDICAL UNIVERSITY, CHINA

DEPARTMENT OF BIOMATHEMATICS AND BIOSTATISTICS
BEIJING MEDICAL UNIVERSITY, CHINA

INSTITUTE OF MATHEMATICS AND STATISTICS
CORNWALLIS BUILDING
THE UNIVERSITY CANTERBURY
KENT CT2 7NF, UNITED KINGDOM