ON ANALYSIS OF DECAY-TYPE DATA

By

Umed Singh

Haryana Agricultural University, Hissar

(Received : March, 1976)

1. Introduction

Many situations in biology, epidemiology, economics and animal drug studies give rise to data that follow a decay-type function with time. This is particularly true in biological radiation, growth and tracer studies. In animal drug studies we have situations where a specified dose of a drug is administered by rapid intraveneous injection to a subject. It is assumed that drug mixes uniformly and instantaneously into blood. Blood samples are taken at different time intervals and analysed chemically for drug concentration at different timings. It was found by Worsley and Lax[5] that polynomial forms do not give a satisfactory fit to such data. The most widely accepted forms are of the type :

$$y(t) = \sum_{j=1}^{m} \alpha_j \; e^{-\lambda_j t} \; + \epsilon(t) \qquad (1.1)$$

where the $\epsilon(t)$ are random errors assumed to be independent with zero means and the parameters α_j & λ_j are assumed to be non-negative. In such cases a knowledge of the time t at which blood samples are taken, determines an ordering, partial or total, of the corresponding mean concentrations, $E[y(t)]=\eta(t)$, say.

In most classical approaches to fitting such models, no notice is taken of the ordered observations. We assume that the regression functions are subject to order restrictions.

Writing $\rho_j=\exp(-\lambda_j)$,

$$y(t)= \sum_{j=1}^{m} \alpha_j \rho_j{}^{t} + \epsilon(t), \qquad (1.2)$$

Let the $(n+1)$ observations be denoted by $y(0)$, $y(1)$,....., $y(n)$ for $t=t_0, t_1,.....t_n$. In the above case of blood levels, of drug,

for $t_0<t_1<t_2<.....<t_n$,

$$E[Y(t_i)]>E[Y(t_j)],\ t_1<t_j,\ i<j,$$

$$i,j=0,\ 1,\ 2,.....,\ n.$$

If there are no order restrictions on $E[Y(t_j)]$, $j=0,\ 1,2,.....,\ n$, the weighted least squares estimates of the parameters in (1.2) are obtained by minimizing,

$$\sum_{i}^{n} w_i[y(t_i)-E(Y(t_i)]^2. \qquad ...(1.3)$$

where w_i are known or unknown weights.

In this paper we fit these regression functions taking into account the order restriction. Antitónic estimates are obtained from basic estimates. Several weighing schemes are examined both on real and simulated data.

2. Antitonic Regression Over a Simply Ordered Finite Set

In this section we define the various functions involved in antitonic regression and state some relevant theorems on antitonic regression. For a comphrehensive survey of antitonic regression, one may refer to Barlow *et al.*[1]

2.1. Definitions

2.1.1. The estimates obtained by minimizing (1.3) will be called the basic estimates of the parameters.

2.1.2. Let T be the finite set $(t_1\ t_2,.....,\ t_n)$ with the simple order $t_1<t_2<...<t_n$. A real valued function f on T is antitonic if $t_i,\ t,$ T and $t_i<t_j$ imply $f(t_i) \geqslant f(t_j)$. Let g be a given function on T and w a given positive function on T. An antitonic function g on T is an antitonic regression of g with weights w with respect to the simple ordering $t_1<t_2<...<t_n$ if it minimizes in the class of antitonic function on T the sum

$$\sum_{t_i \in T} w(t_i)[g(t_i) - f(t_i)]^2$$

and g^* is simply called an antitonic regression of g.

2.2. Graphical and Analytical Procedures

A graphical interpretation of the antitonic regression is illuminating. Assuming the simple ordering $t_1 \leqslant t_2 < \ldots < t_n$ we plot the cumulative sums

$$G_k = \sum_{i=1}^{k} g(t_i) w(t_i) \qquad \ldots(2.1)$$

against the cumulative sums

$$W_k = \sum_{i=1}^{k} w(t_i), \; k = 1, 2, 3, \ldots, n \qquad \ldots(2.2)$$

That is, we plot the points $P_k = (W_k, G_k)$, $k = 0, 1, 2, \ldots, n$, $P_0 = (0,0)$. These points constitute the cumulative sum diagram (CSD) of the given function g with weights w_i. The slope of the segment joining P_{k-1} to P_k is $g(t_k)$, $K = 1, 2, \ldots, n$. It will be seen that the antitonic regression of g is given by the slope of the Least Concave Majorant (LCM) which is the graph of the infimum of all concave functions whose graphs lie above the CSD. The value of the antitonic regression g^* at a point t_k is just the slope of the LCM at the point P_k^* with abscissa

$$\sum_{i=1}^{k} w(t_i)$$

Closely related to the graphical representation of the antitonic regression as the slope of the LCM is the Min—Max Formula

$$g^*(t_i) = \min_{k \geqslant i} \max_{s \leqslant i} AV(s, k), \qquad \ldots(2.3)$$

$$\text{where } \mathrm{Av}(s,k) = \sum_{r=s}^{k} g(t_r)\, w(t_r) \Big/ \sum_{r=s}^{k} w(t_r). \qquad \ldots(2.4)$$

For numerical illustration of these procedures one may refer to Singh.[4]

3. ANTITONIZATION OF BASIC ESTIMATES

If the basic estimates of $E[y(t_i)]$ satisfy the order restrictions, they are antitonic estimates. If not, we replaces $y(t_i)$ by their antitonic regression estimates $y^*(t_i)$ with weights w_i. These estimates will be better than $y(t_i)$, in the sense of least squares. In the case of exponential family, the antitonic regression of the basic estimate turns out to coincide with the maximum likelihood estimates under the order restrictions.

Theorem 3.1

Let η be an unknown function on a finite set T known to be antitonic with respect to a simple order on T. Let $w(t)$, $t \in T$, be a set of positive weights. Let g be an estimate of η. Let g^* be the antitonic regression of g with weights w. Then

$$\sum_t [\eta(t) - g^*(t)]^2 w(t) \leqslant \sum_t [\eta(t) - g(t)]^2 w(t) \qquad ...(3.1)$$

Proof :

The proof is an immediate consequence of the following inequality, valid for all antitonic η :

$$\sum_t [g(t) - \eta(t)]^2 w(t) \geqslant \sum_t [g(t) - g^*(t)]^2 w(t)$$

$$+ \sum_t [g^*(t) - \eta(t)]^2 w(t), \qquad ....(3.2)$$

since η is antitonic and

$$\sum_t [g(t) - g^*(t)]^2 w(t) \geqslant 0,$$

the proof follows.

The procedure for finding antitonic regression is as follows : For a given set of observations $y(t_i)$, $i = 0, 1, 2...n$, we first determine antitonic regression $y^*(t_i)$ of $y(t_i)$.

Having determined the antitonic regression, the estimates of parameters ρ_j and α_j in the model (1.2) are determined. Note that α_j and ρ_j are common to each $\eta(t_i)$. The antitonic estimates of α_j and ρ_j, are given by minimizing the following,

$$\sum_{i=0}^{n} \left[y^*(t_i) - \sum_{j=1}^{m} \alpha_j \rho_j^{t_i} \right]^2 w(t_i) \qquad \ldots(3.3)$$

4. Choice of Weighing Scheme

In this section we shall investigate three weighing schemes for the model (1.2) when errors are assumed to be distributed with equal variances. Let $E[\epsilon^2 (t_i)] = \sigma^2$ for all t_i. In usual least squares analysis we take $w(t_i)$ to be the same for all t_i's but for the model under discussion it may not be the best choice. In this model the coefficient of variation which is an index of the reliability of data rapidly increases with the increasc in the value of t_i and when t_i sufficiently large the error component dominates the fixed component in (1.1). For large values of t_i (depending upon the magnitude of σ^2) the observations contain almost no information about the parameter α_j and ρ_j. In such cases it becomes very essential to have antitonic weights with respect to the independent variable t. Obviously the choice of antitonic weights puts miximum reliance on the initial observations and least reliance on the last observations. If we disregard that there are m fixed components in the model given by equation (1.2) then the simplest antitonic weighing scheme in cast t_i are equi-spaced, is given by

$$w_i = a^{i+1}, \qquad \ldots(4.1)$$

where a is given by

$$\sum_{i=0}^{n} w_i = \frac{a(1-a^n)}{1-a} = 1 \qquad \ldots(4.2)$$

Hence given the number of observations we can uniquely determine the weights to be assigned to each level of t. The above weighing scheme was found to work better in many cases and gave considerably smaller residual sum of squares over the scheme of equal weights. If we assume that $\rho_1 > \rho_2 > \ldots > \rho_m$ then the contribution of the mth

component becomes negligible first as the level of t is increased followed by the next lowest ρ_{m-1} component. Finally beyond certain level of t the contribution of only the slowest moving component is appreciable. Obviously the increase in the level of t beyond certain level depending on the magnitude of slowest moving component does not contain much information about the parameters and it is not advisable to derive a weighing scheme as a function of m. If the ρ parameters are well separated in time then the above proposed weighing scheme is enough. However, if the parameters are not well separated then we may choose weights directly proportional to the observed magnitude of observations, *i.e.*

$$w_i = \frac{|y_i|}{\sum_{i=0}^{n} |y_i|} \qquad \ldots(4.3)$$

Choice of weights according to equation (4.3) amounts to the selection of weights approximately inversely proportional to the coefficient of variation as error variance is assumed to be constant for all t.

5. Examples

In this section we examine the performance of weighing schemes described in section 4 after replacing the basic estimates by their antitonic estimates. Initial estimates of the parameters ρ_j and α_j are obtained by the methods proposed by Singh.[4] Two numerical examples considered are taken from Cornell[2] and Galambos and Cornell.[3] Data for the third example are simulated on electronic computer.

Example 5.1

In order to examine the performance of weighted least squares estimation with antitonic weights over the ordinary least squares estimation procedure, we consider the set of a simulated data given in Table 1 obtained by simulated regression model given in (1.2) for $m=2$.

TABLE 1

Simulated Data

t	0	1	2	3	4	5
y (t)	0.99580	0.86755	0.75378	0.68462	0.58998	0.49806
t	6	7	8	9	10	11
y (t)	0.49066	0.35738	0.31896	0.32844	0.24684	0.29593
t	12	13	14	15	16	17
y (t)	0.18045	0.25398	0.17297	0.16266	0.15076	0.12821
t	18	19	20	21	22	23
y (t)	0.12233	0.15341	0.13334	0.09083	0 09683	0.09450

The error mean squares for the iterative least squares estimation were found by fitting the model (1.2) with $m=2$ and are given below for the two weighing schemes:

Weighing Scheme	*Error Mean Squares*
Equal Wts	0.000,735,94
Weights $w_t \propto a^{t+1}$	0.000,624,26

That is the reduction in Error Mean Squares is 0.000,111,68 which is about 18% by using the scheme (4.1).

Example 5.2

The following numerical example illustrated the application of the model:

$$y(t)=\alpha_1\rho_1^t+\alpha_2\rho_2^t+\epsilon(t) \qquad \ldots(5.1)$$

using the data of Table 2 given by Cornell[2]. The observations describe the distribution of background pulses generated in a proportional counter by neutron interaction with the walls and gas plus pulses due to circuit noise. The heights t are recorded at equi-spaced intervals.

TABLE 2

Logarithms y (t) of Frequencies of Pulse Heights t Generated in a Proportional Counter

t =	0	1	2	3	4	5	6	7
y (t) =	10.430	4.703	2.327	1.140	0.615	0.325	0.170	0.117
t =	8	9	10	11	12	13	14	15
y (t) =	0.05	0.04	0.046	0.022	0.036	0.021	0.018	0.016

Three following weighing schemes were adopted and the error mean squares are as below :

Weighing Scheme	*Error Mean Square*
Equal weights	0.000,351,61
Weights $w_i \alpha a^{t+1}$	0.000,243,71
Weights $w_i \alpha \mid y(i) \mid$	0.000,121,35

A reduction in error mean squares varying from 31% to 65% is accomplished by choosing appropriate antitonic weights.

Example 5.3

A study was undertaken by Galambos and Cornell[3] to develop a mathematical model to describe sulphate metabolism humans. The data given in Table 3 gives proportions of radioactive counts of blood at various times in hours following the injection.

TABLE 3

Data on Proportions y_i of Radioactive Tracer at Various Times t_i

i =	2	3	4	5	6	7	8	9
t_i =	2	3	5	8	12	24	48	72
y_i =	0.84	0.79	0.64	0.55	0.44	0.27	0.12	0.06

The model given in (1.2) with m=2 was fitted with three different weighing schemes and the results obtained are as below :

Weighing Scheme	*Error Mean Squares*
Equal Weights	0.000,819,33
Weights $w_i \propto a^{i+1}$	0.000,115,73
Weights $w_i \propto \lvert y_i \rvert$	0.000,053,29

As is clear from the above figures, a considerable reduction in error mean squares is accomplished by choosing appropriate antitonic weights.

If errors $\epsilon(t)$ are assumed to be independent with unequal variances σ_t^2. In the usual least squares analysis, we minimize

$$\sum\left[\frac{y(t)-\mathrm{E}\,y(t)}{\sigma_t}\right]^2 \qquad \ldots(5.2)$$

that is, the weights w_t are $\frac{1}{\sigma^2_t}$, $t=0, 1, 2, \ldots, n$. In case of equal variance the choice of antitonic weights is motivated by the index of coefficient of variation, in this case the choice of

$$w_t = \frac{1}{\sigma^2_t}$$

takes care of this fact and no new scheme of weights is proposed.

6. Summary

This paper describes a technique for analysing data of decay-type with order restrictions with special reference to the use of tracers in

biological systems. The method antitonizes the basic estimates. Several weighing schemes are examined for estimating the non-linear and the linear parameters both on real and simulated data. Considerable improvement in estimates is found by this technique in both situations.

7. Acknowledgement

The author wishes to express his appreciation to the Ohio State University, Columbus, Ohio for providing computer facilities for this research.

References

[1] Barlow, R.E. ; Bartholomew, D.J. ; Bremner, J.M. ; and Brunk, H.D. (1972). *Statistical Inference Under Order Restrictions.* Wiley, New York.

[2] Cornell. R.G. (1962). A method for fitting linear combinations of exponentials. *Biometrics* 18, 104-13.

[3] Galambos, J.T., and Cornell, R.G. (1962). Mathematical Models for the study of metabolic pattern of sulphate. *J. Lab. and Clinical Medicine* 60, 53-63.

[4] Singh, Umed (1975). *Contributions to Statistical Studies of Compartmental Models.* Unpublished Ph. D. dissertation. The Ohio State University, Columbus.

[5] Worsley, B.H., and Lax, C.A. (1962). Selection of a numerical technique for analysing experimental data of the decay-type with special reference to the use of tracers in biological systems. *Biochem. Biophys. Acta* 59, 1-24.