AUG 25 1965

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MASTER

THE USE OF NON-LINEAR REGRESSION METHODS FOR
ANALYSING SENSITIVITY AND QUANTAL RESPONSE DATA*

R. H. Moore and R. K. Zeigler
University of California
Los Alamos Scientific Laboratory
Los Alamos, New Mexico

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A great many special methods for the statistical analysis of sensitivity or quantal response data have been developed during the past century. This paper demonstrates that many of these techniques can be considered in the light of non-linear regression methods which have been made more tolerable in recent years with the prevalence of high-speed computers.

*Work performed under the auspices of the U. S. Atomic Energy Commission.

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1. INTRODUCTION

Sensitivity and quantal response methods are used in many scientific fields. They are concerned with the statistical analysis of data that are obtained by subjecting a test item to a known level of stimulus (an insect is given a certain amount of poison, an explosive is dropped a predetermined number of feet) and noting whether the test item responds (dies, explodes) to that level or does not respond (lives, does not explode). A series of such experiments is carried out on different test items until several levels of stimulus are encountered at which some respond and some do not.

Perhaps the best-known technique is that of probit analysis, described by Finney (1952). The "up and down" method, described by Dixon and Mood (1948), is widely used and has an advantage (compared with probit analysis) of being non-iterative, but it does suffer some loss of efficiency. These methods are both designed to estimate parameters by the method of maximum likelihood, an idea still employed in fairly recent investigations (Ashford and Smith, 1964). It is appropriate to mention an estimating procedure by Brownlee, et al., (1953), which is designed for small samples and is based on a stochastic process concept rather than maximum likelihood.

The purpose of this paper is to emphasize the fact that the methods which are based on maximum likelihood can be formulated as non-linear regression problems. Several examples are presented to demonstrate the effectiveness of regression methods.

2. MAXIMUM LIKELIHOOD ESTIMATION

The following line of reasoning leads to the maximum likelihood equations. It is assumed that each test item is randomly selected from some larger population. It is further assumed that each item has associated with it a level of stimulus below which it will not respond and above which it will respond. This level may be called the threshold of the item. Finally, it is supposed that the thresholds of the population of items are distributed according to a density function $f(t ; \alpha)$ where α is a vector of k parameters which are of interest. Thus, if a randomly selected item is subjected to a level of stimulus, say x , the probability that it will respond may be written

$$\Pr(t < x) = \int_{-\infty}^x f(t ; \alpha) dt = F(x ; \alpha) . \quad (1)$$

It is common, and sometimes reasonable, to assume that the tolerance density is normal, so that

$$\Pr(t < x) = \int_{-\infty}^x (2\pi)^{-1/2} \sigma^{-1} \exp \left\{ -\frac{1}{2} \left(\frac{t - \mu}{\sigma} \right)^2 \right\} dt \quad (1')$$

and μ and σ are the parameters to be estimated. It is not the intent of

this paper to discuss the choice of the appropriate form that Equation (1) should have for a particular application. Probits (Finney, 1952), normits (Berkson, 1957), and logits (Berkson, 1953) all have their advocates and users.

The usual procedure leading to the likelihood estimates is to select a set of levels of stimulus $x_1, x_2, \dots, x_i, \dots, x_m$. A number of items, say n_i , are tested at the level x_i , r_i of which respond. If the probability of a single item responding at x_i is $P_i(\alpha) = F(x_i; \alpha)$, then $p_i = r_i/n_i$ is an estimate of $P_i(\alpha)$. Since the tests are assumed to be independently performed, the probability of obtaining the m results $p_1, p_2, \dots, p_i, \dots, p_m$ can be expressed as

$$P = \sum_{i=1}^m \binom{n_i}{r_i} P_i^{r_i} (1 - P_i)^{n_i - r_i} \quad (2)$$

where it must be remembered that P_i is a function of the parameters of the threshold density function.

The likelihood equations which must be solved are (cf. Finney, 1952, Appendix II)

$$\frac{\partial \ln P}{\partial \alpha_j} = \sum_{i=1}^m \frac{n_i (p_i - P_i)}{P_i (1 - P_i)} \frac{\partial P_i}{\partial \alpha_j} = 0, \quad j = 1, 2, \dots, k. \quad (3)$$

These equations generally are non-linear in the parameters and are commonly solved by iterative methods. The straight line fitting involved in probit, normit, and logit analysis is merely a device to provide initial estimates of the parameter vector α and to make each iteration somewhat more palatable. That such methods were and are effective, however, cannot be overlooked or overstated. A great deal of work was expended in preparing auxiliary tables needed for use when the calculations were being performed by hand or on a conventional desk calculator.

The variances and covariances of the maximum likelihood estimates may be obtained in the usual manner by inverting the matrix A whose element in the j th row and j' th column is

$$a_{jj'} = -E(\partial^2 \log P / \partial \alpha_j \partial \alpha_{j'}) . \quad (4)$$

In practice, of course, this matrix is estimated by evaluating these second partial derivatives using the maximum likelihood estimates of the parameters.

3. NON-LINEAR REGRESSION ESTIMATION

In the formulation of the general regression problem, it is common to assume that the data follow the model

$$y_i = g(z_i ; \beta) + e_i , \quad i = 1, 2, \dots, M \quad (5)$$

where the y_i are observed random variables, z_i is a vector of associated known mathematical variables, β is a vector of unknown parameters to be estimated, and e_i is a random variable whose expected value is zero and whose variance is σ_i^2 . Any pair of the random variables, say $e_{i'}$ and $e_{i''}$ ($i' \neq i''$), are assumed to have zero covariance. If there are K parameters in the vector β , they are normally estimated by minimizing the weighted sum of squares

$$Q = \sum_{i=1}^M w_i [y_i - g(z_i ; \beta)]^2 \quad (6)$$

by solving the normal equations

$$\frac{\partial Q}{\partial \beta_j} = -2 \sum_{i=1}^M w_i [y_i - g(z_i ; \beta)] \frac{\partial g(z_i ; \beta)}{\partial \beta_j} = 0 \quad j = 1, 2, \dots, K \quad (7)$$

for the parameters. The Gauss-Markoff theorem states that, if $g(z_i ; \beta)$ is linear in β and $w_i = 1/\sigma_i^2$, the best linear unbiased estimate of β is obtained from the solution of Equations (7). Consequently, even when the model is non-linear in the parameters, it seems to be standard practice to set the weight equal to the reciprocal of the variance.

The usual procedure for estimating the covariance matrix for the

estimates of the regression parameters is to invert the matrix β whose elements are

$$b_{jj'} = \sum_{i=1}^M w_i \frac{\partial g(z_i; \beta)}{\partial \beta_j} \frac{\partial g(z_i; \beta)}{\partial \beta_{j'}}, \quad j, j' = 1, 2, \dots, K. \quad (8)$$

As with the maximum likelihood covariance matrix, the elements $b_{jj'}$ are in practice evaluated at the estimates of the parameters before the matrix is inverted.

Much effort in recent years has been devoted to obtaining improved methods for minimizing (6) when the parameters appear non-linearly (cf. Hartley, 1961 and Marquardt, 1963). This effort has been fostered by dissatisfaction with the basic Gauss linearization procedure, and it has been stimulated by the availability of computers which make such investigations feasible. Most computer facilities, therefore, have available non-linear regression programs designed to solve Equations (7) (e.g., Moore and Zeigler, 1959). Useful programs of this type allow w_i to be a known function of the parameters, so that the values of the weights may be modified as the iterations proceed.

That Equations (3) and (7) are equivalent should be clear with the use of $g(z_i; \beta) = P_1(\alpha)$, $y_i = p_i$, and $\sigma_i^2 = 1/w_i = P_1(1 - P_1)/n_i$. Thus, if sensitivity or quantal response data are submitted to a program designed to solve the non-linear regression problem and a solution is obtained, that

solution is the maximum likelihood estimate of the parameter vector.

4. COMMENTS

(1) The relationship between maximum likelihood and least squares estimates has been noted by Berkson (1956). However, his discussion is somewhat clouded by the requirement that the function be linear in the parameters and the introduction of several forms of functions to be minimized, all of which are given the generic name χ^2 .

(2) Quite recent work by Cramer (1964), reporting a sampling study of the behavior of estimates obtained from sensitivity data, made use of standard "minimum normit" methods with no apparent modernization in the non-linear regression manner.

(3) It is to be noted that nothing in the development of Equations (3) requires that n_1 be greater than unity. Thus, data in which the levels of the stimulus cannot be predetermined, such as the one involving the penetration of armour by projectiles described by Golub and Grubbs (1956), are simply a routine matter for the non-linear regression approach. A slight difficulty occurs in obtaining initial estimates of the parameters.

(4) With respect to the comment in the preceding paragraph, it is necessary that the data exhibit at least one "cross-over" level; i.e., there must be at least one level of stimulus at which a lack of response occurs which is higher than the lowest level at which response does occur. Without this cross-over, unique parameter estimates usually cannot be obtained.

5. SOME EXAMPLES

In the following examples, reference to the IASL program means the computer program used extensively at the Los Alamos Scientific Laboratory for least squares problems (Moore and Zeigler, 1959). Results are reported to the same number of figures as used by the original presenters of the examples, even though the IASL program was required to solve the least squares equations to at least seven, and sometimes eight, significant figures. The convergence criterion in the IASL program when operated on an IBM 709⁴ (which has slightly more than eight-digit single-precision accuracy) required that the estimated corrections at any iteration be less than 10^{-6} of the current values of the parameters.

Example 1. Perhaps the best known example (because of its appearance in a pioneering text) of probit analysis is concerned with the effect of a series of concentrations of rotenone sprayed on the chrysanthemum aphid (Finney, 1952, pp. 25-55). The data are repeated in Table I.

TABLE I

Toxicity of Rotenone to Chrysanthemum Aphid

Concentration (mg/l)	Log concentration (x_i)	n_i	r_i
10.2	1.01	50	44
7.7	0.89	49	42
5.1	0.71	46	24
3.8	0.58	48	16
2.6	0.41	50	6
0	--	49	0

As is typical of this type of experiment, the assumption was made that the common logarithms of the thresholds was normally distributed with mean μ and standard deviation σ . The IASL program was given the concentrations of Table I and computed the common logarithms for the remainder of the calculation, while the logarithms used in the reference (after some manipulation) were $\hat{\mu}_F = 0.686(\hat{\sigma}_{\hat{\mu}_F} = 0.0220)$ and $\hat{\sigma}_F = 0.239(\hat{\sigma}_{\hat{\sigma}_F} = 0.0267)$, while the IASL program directly gave $\hat{\mu}_L = 0.685(\hat{\sigma}_{\hat{\mu}_L} = 0.0221)$ and $\hat{\sigma}_L = 0.237(\hat{\sigma}_{\hat{\sigma}_L} = 0.0271)$. The discrepancies clearly are small and attributable to the two methods of calculation being performed to differing degrees of precision.

Example 2. An example of the situation in which the values of x_i cannot be preselected has been mentioned in the third comment in Section 4. A tabulation of a set of results is given in Table II (Golub and Grubbs, 1956, pp. 261-265). The penetrating velocities were assumed to be normally distributed, as in the model (1').

TABLE II

Velocities and Conditions of Impact of a Given Projectile

Fired at a Given Armour Plate

<u>Velocity (f/s)</u>	<u>Condition of Impact</u>
2433	Non-Penetration ($n_1 = 1, r_1 = 0$)
2415	Non-Penetration ($n_2 = 1, r_2 = 0$)
2415	Non-Penetration ($n_3 = 1, r_3 = 0$)
2453	Penetration ($n_4 = 1, r_4 = 1$)
2423	Penetration ($n_5 = 1, r_5 = 1$)

Using initial estimates $\mu_0 = 2435$ and $\sigma_0 = 17$, the reported results were $\hat{\mu}_G = 2431.6(\hat{\sigma}_{\mu_G} = 10.7)$ and $\hat{\sigma}_G = 15.0(\hat{\sigma}_{\sigma_G} = 12.5)$ with an estimated covariance of 50.8. The LASL program gave $\hat{\mu}_L = 2431.6(\hat{\sigma}_{\mu_L} = 10.6)$ and $\hat{\sigma}_L = 14.9(\hat{\sigma}_{\sigma_L} = 12.0)$ with an estimated covariance of 46.6.

Example 3. Exploding bridge wire detonators are designed so that the application of an electrical current through a fine wire will cause the wire to burst with enough force to initiate the explosive load in the detonator. The burst current, I_b , is the number of amperes occurring at the time the voltage across the wire is at its maximum. The burst current may or may not be sufficient to cause the detonator to explode. Moreover, the value of the burst current varies from detonator to detonator and cannot be accurately predicted prior to the actual firing of the detonator. The data in Table III show the results of one set of experiments on a particular type of detonator tested in a particular firing setup. They were provided by J. H. Blackburn of Group GMX-7 of the Los Alamos Scientific Laboratory. Again, the model (1') was assumed.

TABLE III

Burst Currents and Results of Detonator Testing

<u>i</u>	<u>Burst Current (amps)</u>	<u>Fired?</u>
1	369	Yes
2	391	Yes
3	370	Yes
4	370	No
5	375	No
6	343	No
7	370	Yes
8	356	No
9	343	No
10	338	No
11	372	Yes
12	352	No
13	359	No
14	356	Yes
15	361	Yes
16	368	Yes
17	347	No

Based on the observations, the initial estimates $\mu_0 = 365$ and $\sigma_0 = 5$ were used. After seven iterations, the IASL program had covered to eight figures. Because it is scarcely sensible to report such results, the estimates were rounded to $\hat{\mu}_L = 363.0$ ($\hat{\sigma}_{\mu_L} = 4.5$) and $\hat{\sigma}_L = 12.6$ ($\hat{\sigma}_{\sigma_L} = 5.7$) with an estimated covariance of 1.5.

Example 4. Dixon and Mood (1948) illustrate the up and down method with a set of "mocked up" data which constitute a sample of size 60 from a normal distribution with $\mu = 1.3$ and $\sigma = 0.2$. Their observations are

repeated in Table IV, where the term "normalized height" is used to indicate these data might have come from an experiment in which explosives are dropped certain distances and a response is an explosion.

TABLE IV
Dixon and Mood "Data"

Normalized Height	Number of	
	Explosions	Non-Explosions
2.0	1	0
1.7	10	0
1.4	18	9
1.1	2	18
0.8	0	2

As indicated in the Appendix to their paper, Dixon and Mood begin by setting up the likelihood function which can be shown to have the same form as Equation (2). Their results are $\hat{\mu} = 1.32(\hat{\sigma}_{\hat{\mu}_D}^2 = 0.035)$ and $\hat{\sigma}_D = 0.17(\hat{\sigma}_{\hat{\sigma}_D}^2 = 0.039)$, while the IASL program gave $\hat{\mu}_L = 1.32(\hat{\sigma}_{\hat{\mu}_L}^2 = 0.035)$ and $\hat{\sigma}_L = 0.17(\hat{\sigma}_{\hat{\sigma}_L}^2 = 0.038)$.

References

1. Ashford, J. R. and Smith, C. S. 1964. General models for quantal response to the joint action of a mixture of drugs. Biometrika 51, 413-428.
2. Berkson, J. 1953. A statistically precise and relatively simple method of estimating the bio-assay with quantal response, based on the logistic function. J. Amer. Stat. Assn. 48, 565-599.
3. Berkson, J. 1956. Estimation by least squares and by maximum likelihood. In Proceedings of the Third Berkeley Symposium on Mathematical Statistics and Probability, Vol. I, edited by J. Neyman, University of California Press, Berkeley, 1-11.
4. Berkson, J. 1957. Tables for use in estimating the normal distribution function by normit analysis. Biometrika 44, 411-435.
5. Brownlee, K. A., Hodges, J. L., Jr., and Rosenblatt, M. 1953. The up-and-down method with small samples. J. Amer. Stat. Assn. 48, 262-277.
6. Cramer, E. M. 1964. Some comparisons of methods of fitting the dosage response curve for small samples. J. Amer. Stat. Assn. 59, 779-793.
7. Dixon, W. J. and Mood, A. M. 1948. A method for obtaining and analyzing sensitivity data. J. Amer. Stat. Assn. 43, 109-126.

8. Finney, D. J. 1952. Probit Analysis, 2nd ed. University Press, Cambridge.
9. Golub, A. and Grubbs, F. E. 1956. Analysis of sensitivity experiments when the levels of stimulus cannot be controlled. J. Amer. Assn. 51, 257-265.
10. Hartley, H. O. 1961. The modified Gauss-Newton method for the fitting of non-linear regression functions by least squares. Technometrics 3, 269-280.
11. Marquardt, D. W. 1963. An algorithm for least squares estimation of non-linear parameters. S.I.A.M. Journal 11, 431-441.
12. Moore, R. H. and Zeigler, R. K. 1959. The solution of the general least squares problem with special reference to high-speed computers. Los Alamos Scientific Laboratory Report LA-2367.