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Random effect models in nonlinear regression with applications to bioassay

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Summary

Transformation and weighting techniques are applied to dose-response curve models. In particular, weighting methods derived from a controlled variable random effect model and a closely related random coefficient model are studied. These two models correspond to additive and multiplicative effects of variations in the dose, and they both lead to variance components proportional to the square of the derivative of

the response function with respect to dose. When the dose-response curve is nonlinear in dose, the variance components are typically identifiable even without replicate measurements of dose. In a bioassay example the fit of a logistic model is studied. The transform both sides technique with a power transformation is shown to give a vast improvement in fit, compared to the analysis with no transformation and no weighting, and it also gives considerably better estimates of the parameters in the logistic function. For the data set studied, a significant further improvement in the fit is possible by use of the random effect models.

Key words: Berkson's controlled variable model; Dose-response curves; Herbicide effects; Heteroscedasticity; Logistic model; Power transformations; Random coefficients; Transform both sides.

1. Introduction

Suppose that we have observations consisting of pairs (x,y), where x is a dose and y a response. The systematic part of the dose-response model is given by

$$y = f(x,\beta), \tag{1.1}$$

e. g. based on a theory or empirical knowledge from the particular field of application. We assume that the main object of the statistical analysis is to estimate the parameter vector β and to test hypotheses with respect to β, typically corresponding to possible simplifications

of the model. An accurate model for the error structure is essential if we want efficient estimates and correct standard errors and p-values, but as will be shown it might also give information on the biological mechanisms involved.

One example of a relation of type (1.1) is the logistic model,

$$y = C + (D-C)[1 + (x/x_0)^{\alpha}]^{-1} \tag{1.2}$$

often employed in bioassay and radioimmunoassay, see e. g. Finney (1976, 1978) and De Lean, Munson and Rodbard (1978). It is further used in the analysis of herbicide effects (Grover, Morse and Huang, 1983, and Streibig, 1987), and our main example analysed in Section 3 below is taken from this field.

The problem discussed in this paper is application of transform-both-sides (TBS) and weighting methods, see Carroll and Ruppert (1984, 1987), to nonlinear regression, in particular when there are random effects with respect to a design variable or random coefficients. The main application that we consider is analysis of dose-response curves, and specifically we assume that x is univariate. However, the methods should be useful also for other types of nonlinear regression models, and generalization to multivariate x is possible.

The basic TBS model starting from the relation (1.1) takes the form

$$h(y,\lambda) = h(f(x,\beta),\lambda) + \sigma\epsilon, \tag{1.3}$$

where ϵ has zero mean and unit variance and $h(.,\lambda)$ is a family of transformations depending on the parameter λ, e. g. the Box-Cox (1964) power transformation family

$$h(y,\lambda) = (y^{\lambda} - 1) / \lambda \quad \text{for } \lambda \neq 0 , \tag{1.4}$$

$$h(y,\lambda) = \log(y) \quad \text{for } \lambda = 0 .$$

TBS models are very useful when there is a large quotient between the

maximum and the minimum response as is often the case for dose-response data. Thus, in the example in Section 3 the model (1.3) gives a much better fit than the untransformed model

$$y = f(x,\beta) + \sigma\epsilon. \tag{1.5}$$

An alternative to the TBS model (1.3) is the weighting model

$$y = f(x,\beta) + \sigma\, g(x,\beta,\theta)\, \epsilon, \tag{1.6}$$

where g is supposed to be known except for β and θ. If σ is small, then (1.3) - (1.4) is nearly equivalent to (1.6) with g a power function of the mean, that is $g(x,\beta,\theta) = (f(x,\beta))^{\theta}$ (Carroll and Ruppert 1984). The two methods may be combined to

$$h(y,\lambda) = h(f(x,\beta),\lambda) + \sigma\, g(x,\beta,\theta)\, \epsilon, \tag{1.7}$$

which gives a very flexible model. The advantage of (1.7) over TBS is that (1.7) can model a variance that depends on x as well as on the mean response. By use of a power function in x for g, i. e. $g(x,\beta,\theta) = x^{\theta}$, the model (1.7) is thus shown in Carroll, Cressie and Ruppert (1987) to include most of the current methods for the analysis of the Michaelis-Menten relation

$$y = Vx/(K+x),$$

and in some examples the method with variable λ and θ is shown to give a substantial improvement of fit. A disadvantage of this model is that the parameter θ has no apparent biological interpretation.

In Section 2 we shall study models with additive random effects in x or random coefficients with respect to the effect of x. The two types of models are similar but not identical. Both models lead to functions $g(x,\beta,\theta)$ in (1.6) and (1.7) that depend quadratically on the partial derivative $f_x(x,\beta)$ of $f(x,\beta)$ with respect to x, and the logistic model (1.2) is particularly useful for an empirical study of how these

modifications may improve the fit. The reason is that for this model f_x is close to zero both for small x and for large x but is numerically large in a region in the middle. This makes random effects in x distinguishable from random variation in y.

An important property of the approach described in Section 2 is that it leads to heteroscedastic models with parameters that have biological or physical interpretations.

An example with bioassay data is studied in some detail in Section 3. It is shown that the TBS model (1.3) - (1.4) gives a reasonably good fit, but a closer study of the absolute residuals show that they are on the average smaller both for large and for small x compared to their values in the middle region where $|f_x|$ is large. This suggests that the models in Section 2 might improve the fit, which turns out to be the case. As mentioned above this approach leads to models for the error structure that make sense from a biological point of view, and it is possible to compare the amounts of variability from different sources.

From a practical point of view, two conclusions may be drawn from the study reported in this paper. Firstly, the transform-both-sides method with the power transformation seems to perform well for the logistic model in bioassay. If there are enough observations, then an additional improvement of fit might be possible by use of random effects models. Secondly, the approach with transformations and different types of weighting is very flexible, and combined with residual plots, it constitutes an effective data analytic tool. To illustrate this aspect we have included several residual plots in Section 3.

2. The models for random effects in x and random coefficients

In the nonlinear regression models (1.3) - (1.7) all sources of variability are represented by a single random variable ϵ. However, some error structures with several variance components can be modeled by the proper definition of g. The methods of defining g are based on Taylor expansions and we thus have to assume that the variance components are small in order to get valid approximations.

Especially for linear models, there is a large literature on more complex error structures, known under various names e. g. errors in the variables, measurement errors, random effects and random coefficients, cf. Madansky (1959), Fisk (1967), Hildreth and Houck (1968), Sprent (1969), Stefanski (1985), and the references therein. We shall limit ourselves to two models that seem particularly relevant for the analysis of dose-response curves. The two models are closely related, both describing random variation in the response as a result of either random variations in the dose or the effects of the dose. In the first case, we consider the so-called controlled variable model and assume additive variations in the dose, cf. (2.1) below, while the variations in the second, the random coefficient model, may be regarded as multiplicative.

By use of first order Taylor expansions we shall obtain heteroscedastic models of the type (1.7) with a function g that depends on the partial derivates h_y and f_x of $h(y,\lambda)$ and $f(x,\beta)$ respectively. Using second order Taylor expansions we will further compute a bias correction term involving also second order partial derivatives.

Somewhat surprisingly the nonlinearity in the dose variable leads to some simplifications: parameters that would have been unidentifiable

for linear models now become identifiable.

2.1 Random effects in a controlled variable model.

Assume that the independent variable has a known value, x, but that the physical or biological system is affected not by x but by

(2.1) $$\tilde{x} = x + \sigma_x \delta,$$

where δ has zero mean and unit variance. In the example in Section 3, x is the concentration of herbicide applied to the plants, while $\tilde{x}$ may be thought of as being proportional to the amount actually absorbed by a plant (per unit of plant volume), or the amount acting in the plant (cf. Hewlett and Plackett, 1979, p. 44). The additive random effect $\sigma_x \delta$ has a variance σ_x^2 that is allowed to depend on x. An essential feature of this model is that under independent repetitions, x is constant but $\tilde{x}$ varies. For this reason the model is called the controlled-variable model (Berkson, 1950).

Let us now use a first order Taylor expansion in (1.3) with x replaced by $\tilde{x}$, and assume that δ and ϵ are independent. We get

$$h(y,\lambda) = h(f(\tilde{x},\beta),\lambda) + \sigma\epsilon \approx$$

$$\approx h(f(x,\beta),\lambda) + h_y(f(x,\beta),\lambda)\ f_x(x,\beta)\ \sigma_x\ \delta + \sigma\epsilon,$$

which gives $Eh(y,\lambda) \approx h(f(x,\beta),\lambda)$ and

(2.2) $$\text{var } h(y,\lambda) \approx \sigma^2\{\ [h_y(f(x,\beta),\lambda)\ f_x(x,\beta)]^2\ \sigma_x^2/\ \sigma^2 + 1\ \}.$$

We are thus lead to a model of type (1.7) with $\sigma^2 g^2$ given by the right member of (2.2).

Consider here briefly the case, where h is the identity transformation, σ_x is constant and the distributions of ϵ and δ are

normal. For a function $f(x,\beta)$ that is linear in x, the error variances σ_x^2 and σ^2 are then non-identifiable, cf. Madansky (1959), but for nonlinear f or non-constant σ_x^2 they may be identifiable.

Let us now assume that h is the power transformation (1.4) and further that

$$\sigma_x = \sigma_1 \, x^{1-\theta}$$

corresponding to a model for errors in x where x^θ has approximate constant variance. Then we get a model of type (1.7) with g given by

$$g(x,\beta,\theta)^2 = 1 + A \, x^{2-2\theta}[f(x,\beta)^{\lambda-1} \, f_x(x,\beta)]^2, \tag{2.3}$$

where $A = (\sigma_1/\sigma)^2$. In the example in Section 3 with the bioassay data and the logistic function for f, this turns out to give the model with the best fit.

As mentioned above, one can also obtain a bias correction by use of a second order Taylor expansion of $h(f(x+\sigma_x\delta,\beta),\lambda)$. We get

$$Eh(y,\lambda) \approx h(f(x,\beta),\lambda) + s(x,\beta,\lambda) \, \sigma_x^2, \tag{2.4}$$

where

$$s(x,\beta,\lambda) = \frac{1}{2} \frac{\partial^2}{\partial x^2}(h(f(x,\beta),\lambda)) \; . \tag{2.5}$$

2.2 A random coefficient model.

Instead of the random effect model obtained from (2.1) we shall now consider a random coefficient model. It is then convenient to write $f(x,\beta)$ in the previous models on the form $f(cx,\beta)$, letting the parameter vector now be (c,β). Note that in (1.2) we have

$$c = 1/x_0 \; .$$

Let us further replace c by

$$\tilde{c} = c + \sigma_c \, \delta,$$

where δ is assumed to be independent of ϵ and has zero mean and unit variance. In the herbicide example, $\tilde{c}$ could vary with the rate of herbicide absorption by plants, and then c would be the average value of $\tilde{c}$ among plants. The mean c may itself vary in a systematic way; in the herbicide study c depends on the type of herbicide. By use of a first order Taylor expansion of

$$h(y,\lambda) = h(f(\tilde{c}x,\beta),\lambda) + \sigma\epsilon$$

we get $Eh(y,\lambda) \approx 0$ and

(2.6) $\text{var } h(y,\lambda) \approx \sigma^2 \{[h_y(f(cx,\beta),\lambda)\ f_x(cx,\beta)]^2\ x^2\ \sigma_c{}^2/\sigma^2 + 1\}$.

Once more we obtain a model of type (1.7); this time with $\sigma^2 g^2$ given by the right member of (2.6).

In particular, if we regard a power transformation and assume that

$$\sigma_c = \sigma_1\ c^{1-\eta},$$

corresponding to approximately a constant variance for c^{η}, we get a model of type (1.7) with g given by

(2.7) $\quad g(x,\beta,\eta)^2 = 1 + A\ x^2\ c^{2-2\eta}[f(cx,\beta)^{\lambda-1}\ f_x(cx,\beta)]^2,$

where $A = (\sigma_1/\sigma)^2$.

If c is constant, e. g. in a herbicide study with a single herbicide, or $\eta = 1$, then (2.7) is a special case of (2.3) with $\theta = 0$. This has practical implications. In the herbicide study, for example, it would tell us that random variation in the herbicide absorption rate may be indistinguishable (even in principle) from an additive random variation in the amount of herbicide absorbed.

As with the random effects model we can obtain a bias correction by use of a second order Taylor expansion. We now get

(2.8) $\quad Eh(y,\lambda) \approx h(f(cx,\beta),\lambda) + s(cx,\beta,\lambda)\ x^2\ \sigma_c{}^2,$

with s given by (2.5). It may be noted that for a function $f(x,\beta)$ that

is linear in x the bias correction terms in (2.4) and (2.8) disappear.

3. An example with bioassay data

In an experiment with 8 herbicides, 6 different nonzero doses

$$x = 2^{j-5},\ j = 0,\ldots,5,$$

were used for each herbicide. Actually the dose is a concentration of herbicide per unit volume of water, but for simplicity we have here scaled x so that the maximal dose for each herbicide is one. In each of three replicates all combinations of herbicides and nonzero doses occurred once together with two observations without any herbicide.

The experiment was performed in growth chambers. Five one-week old seedlings of Sinapis alba L. were grown together in a pot in a nutrient solution during fourteen days. For the nonzero doses the solution also contained one of the following additives: MCPA, 2,4-D, mecoprop, dichlorprop (herbicides 1 - 4) or their commercial formulations (herbicides 5 - 8). Thus the 8 herbicides are naturally grouped into four pairs: (1,5), (2,6), (3,7), and (4,8), and in each pair the two herbicides should have the same active ingredients but different formulation constituents, which were assumed to be biologically inert.

The data analysed below consist of the 150 observations y of dry weights, each observation being the weight of five plants grown in the same pot. Figure 1 shows the 18 points corresponding to one of the herbicides, together with the 6 points corresponding to zero dose. Notice the heteroscedasticity in figure 1: the variance of y appears to be a monotonic function of the mean.

The models discussed are all based on the following logistic dose-response relation as the systematic part of the models

$$f(x,\beta) = C + (D-C)[1 + (x/x_{herb})^{\alpha}]^{-1}, \tag{3.1}$$

where the parameters C and D were the same for all the herbicides. The half-effect parameter x_{herb} was allowed to take different values for each of the herbicides, while the shape parameter α was allowed to take four different values $\alpha_1,\ldots,\alpha_4$ corresponding to the grouping of the herbicides into four pairs. Thus the parameter vector β in (3.1) has 14 components. Beside the systematic part and the error structure, all models considered also contained additive block effects corresponding to the three replicates

We fit (3.1) to the herbicide data by nonlinear least-squares, which, of course, would be maximum likelihood if we had additive, constant variance and Gaussian errors. The log-likelihood is given in Table 1 and the parameter estimates in Table 2 (model 1). In particular, we note that the estimate of C is negative. The residual plot (Figure 2) shows clearly the substantial heteroscedasticity, which was also seen in Figure 1, and a systematic lack of fit for small values of the predicted mean. One might reject the logistic model, but this would be premature. We will see that the problem does not lie in the systematic part of the model but in the error structure. When the observations are properly weighted, the estimate of C is positive and the fit appears much better.

The heteroscedasticity suggests that we use the TBS method to fit the logistic model. The transformation h used in the analyses was the modified power transformation transformation (1.4). The effects of replications τ_{rep} were entered into the models after the transformation

since they were regarded as random effects and expected to behave like the residual error ϵ. Thus the model corresponding to (1.3) takes the form

$$h(y,\lambda) = h(f(x,\beta),\lambda) + \gamma_{rep} + \sigma\epsilon \ .$$

The estimation method used in the analyses was maximum likelihood; see Carroll and Ruppert (1987, chapter 4) for a full discussion of maximum likelihood estimation of the TBS model.

The MLE of λ is .12 (Table 1), which is close to the log transformation. From Table 1 we see that the log-likelihood jumps from 239.7 for the nonlinear least-squares fit (model 1) to 309.9 for the TBS model (model 2), indicating a considerable improvement in fit. Figure 3 gives a plot of the transformed dry weight against dose. From a comparison of Figures 1 and 3 it is evident that the transformation removes heteroscedasticity, but not completely as will be analyzed below. Besides the TBS method we also tried weighting by a power of the mean (POM) or by a power of x (POX). Both methods gave considerable improvements compared to NL (model 1 in Table 1), but the corresponding log-likelihood values (not shown in Table 1) were smaller than for TBS.

Combinations of TBS with either POM or POX gave statistically significant improvements of the log-likelihood value, see the results for models 3 and 4 in Table 1. In Particular TBS-POM gave an improvement from 309.9 to 313.1, corresponding to an approximate χ^2-value of 8.4 with one degree of freedom. The corresponding residual plot is shown in Figure 4, which may be compared with Figure 2. Figure 4 certainly seems less heteroscedastic than Figure 2. However, the variance heterogeneity has not been completely eliminated by the transformation and the weighting by the power of the mean: The

residuals in Figure 4 seem less scattered, when the mean is large or small, compared to when the mean takes an intermediate value. The same effect may be seen in Figure 3 where we only have applied the TBS-method.

To better understand the nature of the residual heteroscedasticity in Figure 4, we grouped the data into equally sized subsets according to the size of the predicted mean (group 1 = 25 smallest predicted means, etc.). Figure 5 displays the boxplots of the absolute residuals for the six groups. The boxplots clearly show what was suggested by Figures 3 and 4; the residual variation is largest were the predicted mean is intermediate in value.

We hypothesize that the residual variation in the untransformed data has two components. The first component has a variation proportional to the mean response. The second component is due to a random effect in x and is related to the derivative of the logistic function with respect to x.

This hypothesis led us to the models of Section 2. The random coefficient model, which we call model 6 in this discussion, had a log likelihood of 322.7 (Table 1). The MLEs of λ and η were -.1 and 1.4 respectively; both of these estimates have large standard errors (Table 1), indicating that jointly they are not well determined.

The controlled-variable model (model 5) had the highest log likelihood of any model tested, 325.1. The MLEs were $\hat{\lambda}$ = -.33 and $\hat{\theta}$ = -.41 (Table 1). The standard errors of λ and log(A) are smaller than for the random coefficient model. Boxplots of the residuals, grouped by the predicted mean, are given in Figure 6. Notice that there is no indication of heteroscedasticity.

Observing that the two random effects models (TBS-RC and TBS-CV in Table 1) gave the best fits, we analyzed how large roles the two variance components play in different regions. In Figure 7 the proportion of the variance component due to x is shown as a function of the mean response (transformed back to the original scale). Except for small doses, that is for large values of the response, we see that the variance component due to x tends to dominate, and this dominance is most pronounced in the region where the response is about 20 % of the response for zero dose.

We also tried to include the bias correction (2.4) in the controlled-variable model, i. e. we applied both (2.3) and (2.4), which gives the same number of parameters as with only (2.3), that is model 5. Astonishingly, it turned out that the likelihood decreased. An explanation might be that in bioassay, the logistic model is not a theoretical model, but a well established empirical model. Hence one could argue that there is no a priori reason for preferring (2.4) as a mean function compared to the mean function without the bias correction.

After one has chosen a model for the error structure one would naturally proceed by analyzing the systematic part of the model. We shall not go into such details here, as it naturally belongs to the special field of applications. Let us only, as an example, give some results testing equality of the shape parameters for the four groups of herbicides, that is $H_0 : \alpha_1 = \alpha_2 = \alpha_3 = \alpha_4$. For the test variable that is approximately χ^2-square distributed with 3 degrees of freedom, the poorly fitting NL-model (model 1 in Table 1) gave the non-significant value 5.2, while the TBS- and TBS-CV-models (models 2

and 5 in Table 1) gave the values 16.5 and 15.4, which both are highly significant.

4. Discussion

For fitting logistic models models in bioassay we have found the transform-both-sides technique with the power family (1.4) highly useful. This is based both on the analysis of the data described in the present paper and other similar data sets from experiments with herbicides, see for instance Streibig (1987). As shown in Section 3 of the present paper it is possible to improve the fit considerably by introducing also a weighting based on the two models for additive or multiplicative random effects of dose defined in Section 2. It is possible that one could have obtained an equally good fit by use of say a weighting function that was a quadratic function of the dose. However, it seems much more preferable to base the weights on a model for the error structure that makes sense from a biological point of view. In the present case one might use the estimates of the variance component due to the random effect of dose and graphs like those in Figure 7 to compare the variability in different types of experiments, for instance different types of media in which the plants are grown.

In the example with the bio-assay data and the logistic model we found a significant improvement in fit by use of the variance component induced by the variations in the dose. However, we did not get any improvement by use of the bias correction. As discussed above in Section 3, this may be due to the fact the logistic model here is an

empirical model. For analysis of data where a good theoretical model exists, we believe that the bias correction might also be useful.

For the example discussed in Section 3 the controlled variable model seems appropriate, but in some other nonlinear regression models it might be more natural to assume an errors-in-variables structure, perhaps with replicate measurements, cf. Dolby and Lipton (1972), Wolter and Fuller (1982) and Johnson and Milliken (1985). It would be interesting to extend the variance component and bias correction methods discussed in the present paper to such models.

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Table 1: Log-likelihood and estimated parameters for the error structure. The models are 1: NL (Nonlinear least-squares fit), 2: TBS (Transform-both-sides), 3: TBS-POM (Transform-both-sides with power of the mean weighting), 4: TBS-POX (Transform-both-sides with power of x weighting), 5: TBS-CV (Transform-both-sides with controlled variable random effect model), 6: TBS-RC (Transform-both-sides with random coefficient model), .

Model	PARAMETER ESTIMATE						Equ	Log-
	$\hat{\lambda}$	POM	POX	$\hat{\theta}$	$\hat{\eta}$	log(A)		likelihood
1 NL							(1.E)	239.699
2 TBS	.117 .074						(1.C)	309.855
3 TBS-POM	-.190 .107	-.349 .119					(1.G)	313.066
4 TBS-POX	.061 .080		.067 .035				(1.G)	311.720
5 TBS-CV	-.333 .115			-.407 .164		1.93 .58	(1.G) (2.E)	325.088
6 TBS-RC	-.098	.158			1.42	2.58 .273	(1.G) 1.01	322.651 (2.G)

Table 2: Estimates of parameters in the logistic model and the block (replicate) effects. The error structure models are: Model 1 - no transformation or weighting, that is, nonlinear least squares. Model 2 - Transform-both-sides. Model 5 - Transform-both-sides with controlled-variable random effect model.

Parameter	Model 1	Model 2	Model 5
D	1.131	1.074	1.046
	.050	.050	.053
C	-.040	.031	.036
	.024	.003	.002
x_1	.066	.067	.070
	.005	.005	.005
x_2	.116	.113	.106
	.025	.015	.010
x_3	.131	.151	.147
	.012	.018	.015
x_4	.223	.217	.225
	.022	.024	.021
x_5	.086	.081	.083
	.004	.005	.005
x_6	.117	.118	.116
	.008	.010	.008
x_7	.130	.116	.125
	.011	.011	.009
x_8	.439	.421	.383
	.081	.069	.056
α_1	2.24	1.96	1.94
	.23	.13	.10
α_2	2.30	2.63	2.43
	.35	.30	.16
α_3	2.16	1.96	2.13
	.30	.15	.17
α_4	1.63	1.71	1.67
	.24	.15	.14

Table 2 (continued)

γ_1	.124	.164	.211
	.023	.040	.048
γ_2	.130	.170	.200
	.026	.042	.050

Figures

Figure 1: Data for one of the 8 herbicides (#3) and zero dose.

Figure 2: Residuals versus predicted means for model 1 (NL in Table 1).

Figure 3: Plot of transformed dry weight for herbicide #3 by use of model 2 (TBS in Table 1).

Figure 4: Residuals versus predicted means for model 3 (TBS-POM in Table 1)

Figure 5: Boxplot for model 3 (TBS-POM in Table 1).

Figure 6: Boxplot for model 5 (TBS-CV in Table 1).

Figure 7: Relative size of variance component due to random effect of dose for models 6 and 5 (TBS-RC and TBS-CV in Table 1).

Fig 1

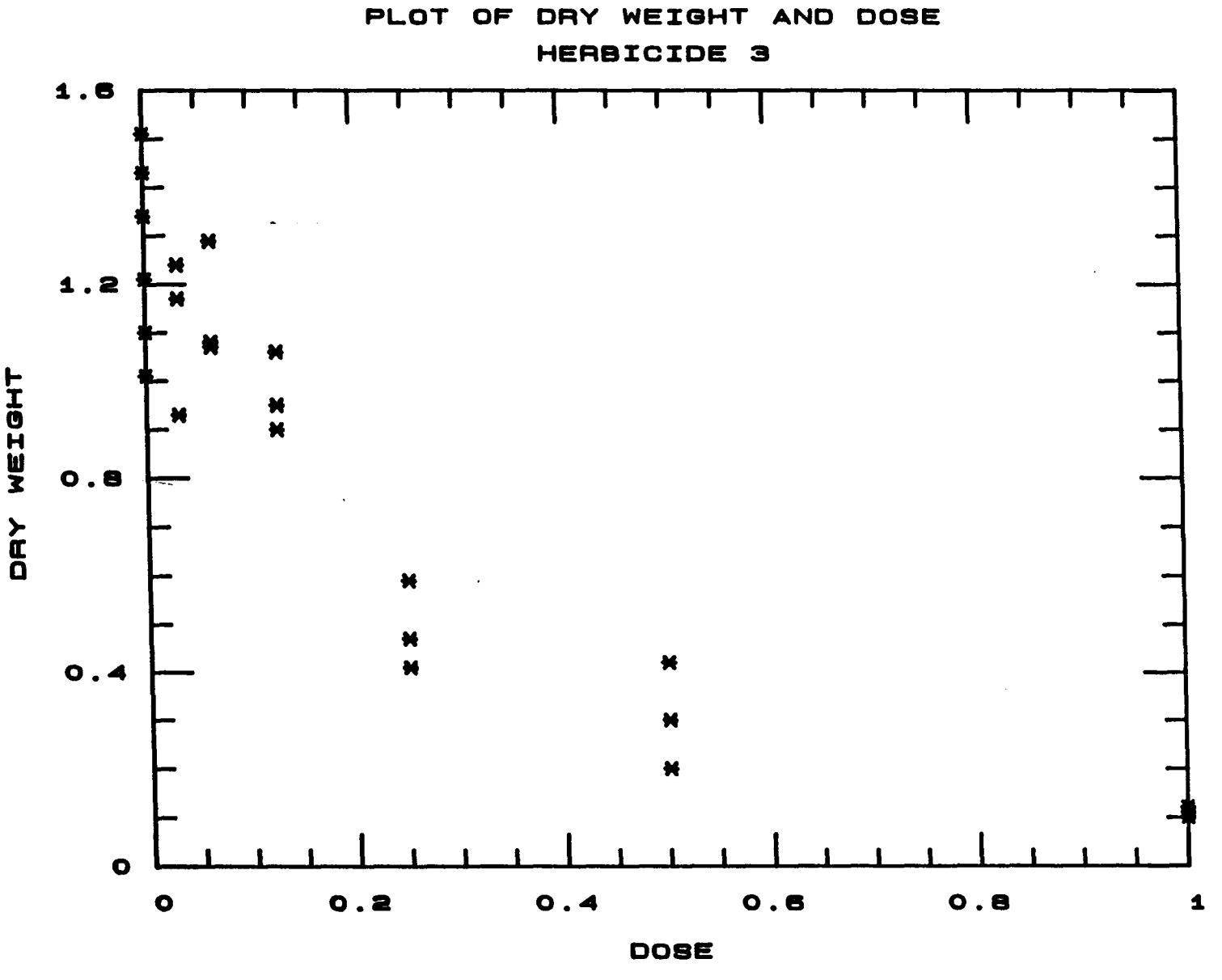

PLOT OF DRY WEIGHT AND DOSE
HERBICIDE 3
DRY WEIGHT
1.6
1.2
0.8
0.4
0
0
0.2
0.4
0.6
0.8
1
DOSE

fig 2

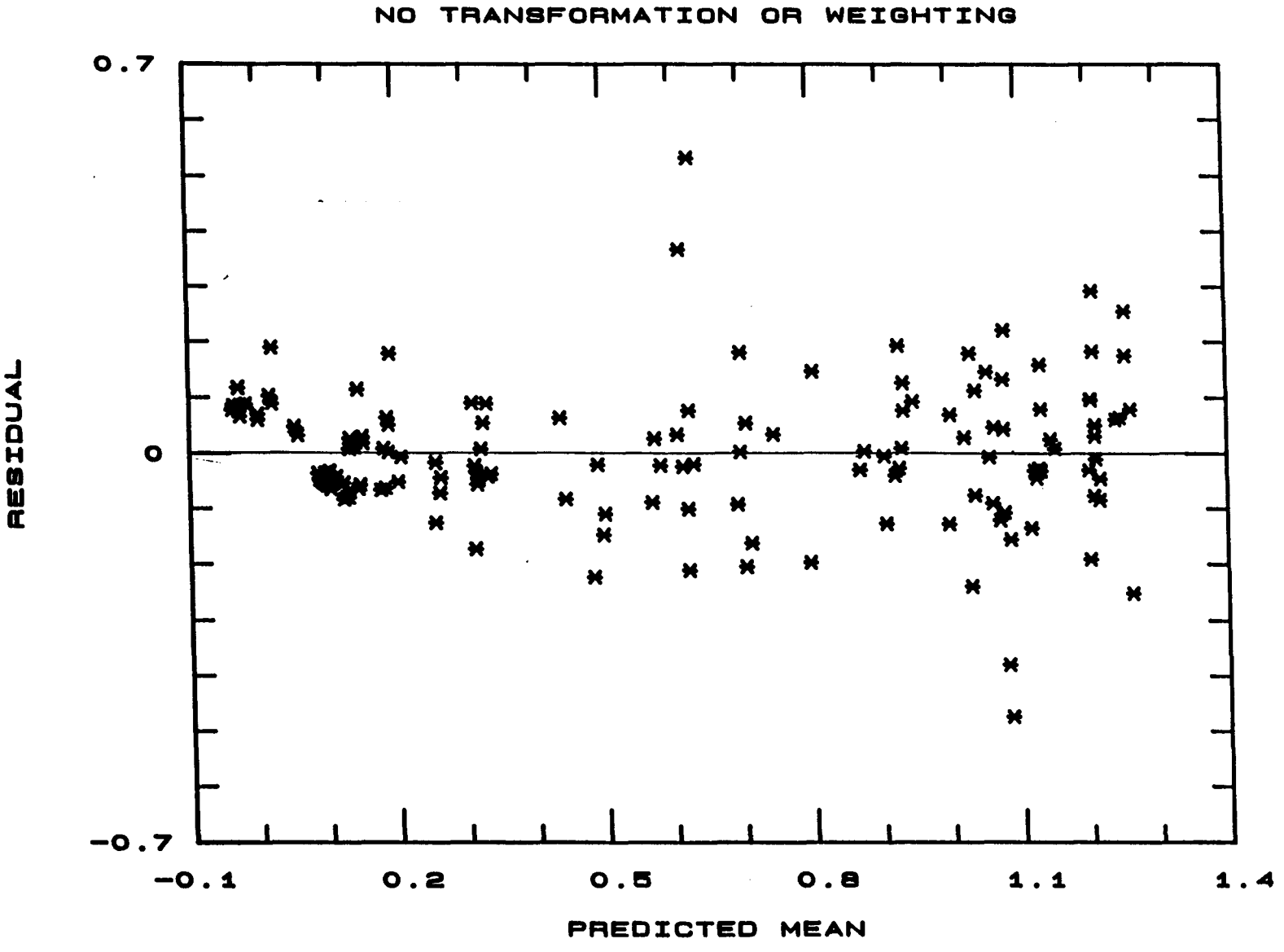

NO TRANSFORMATION OR WEIGHTING
0.7
0
-0.7
RESIDUAL
-0.1
0.2
0.5
0.8
1.1
1.4
PREDICTED MEAN

Fig 3

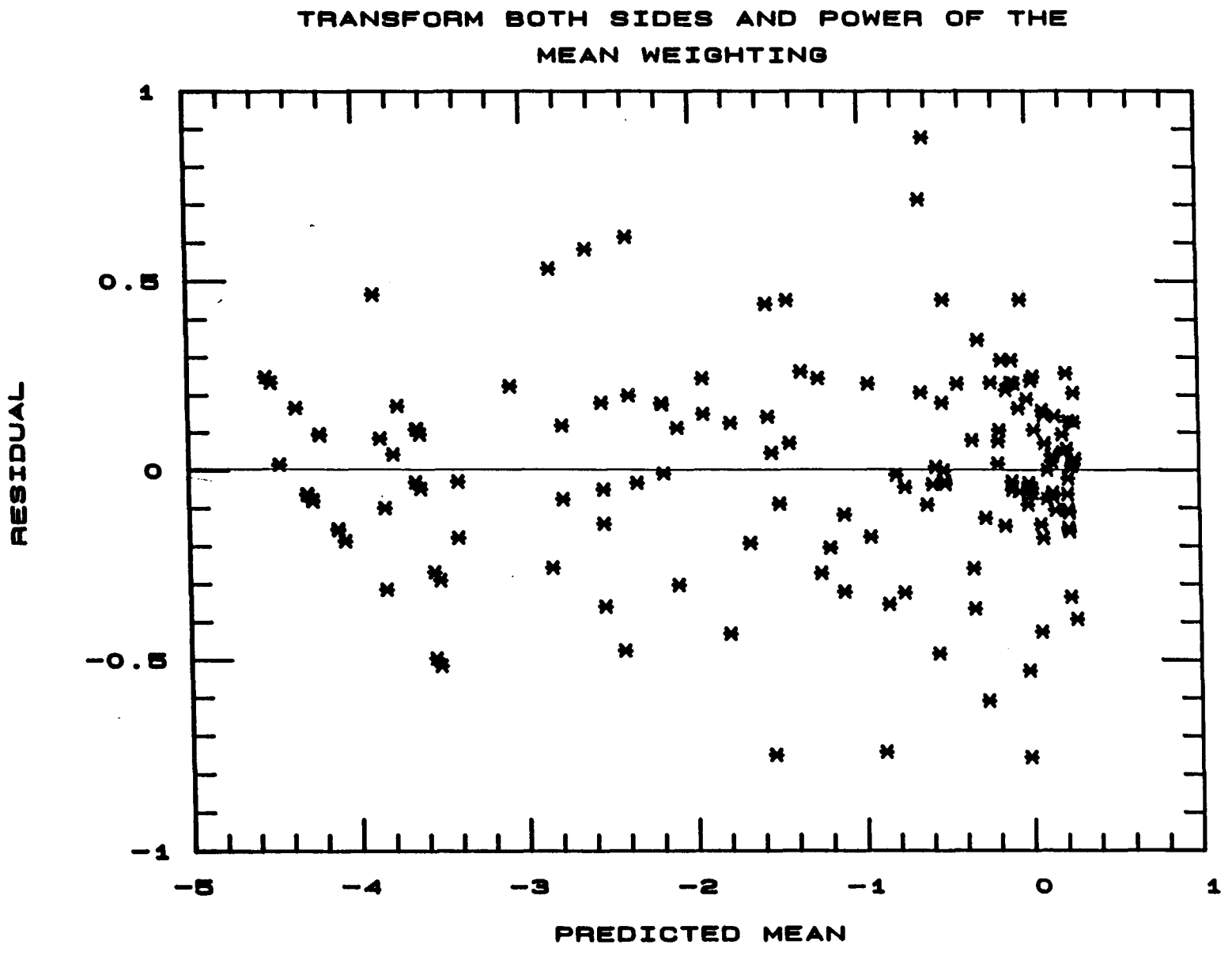

TRANSFORM BOTH SIDES AND POWER OF THE MEAN WEIGHTING
RESIDUAL
1
0.5
0
-0.5
-1
-5
-4
-3
-2
-1
0
1
PREDICTED MEAN

Fig 4

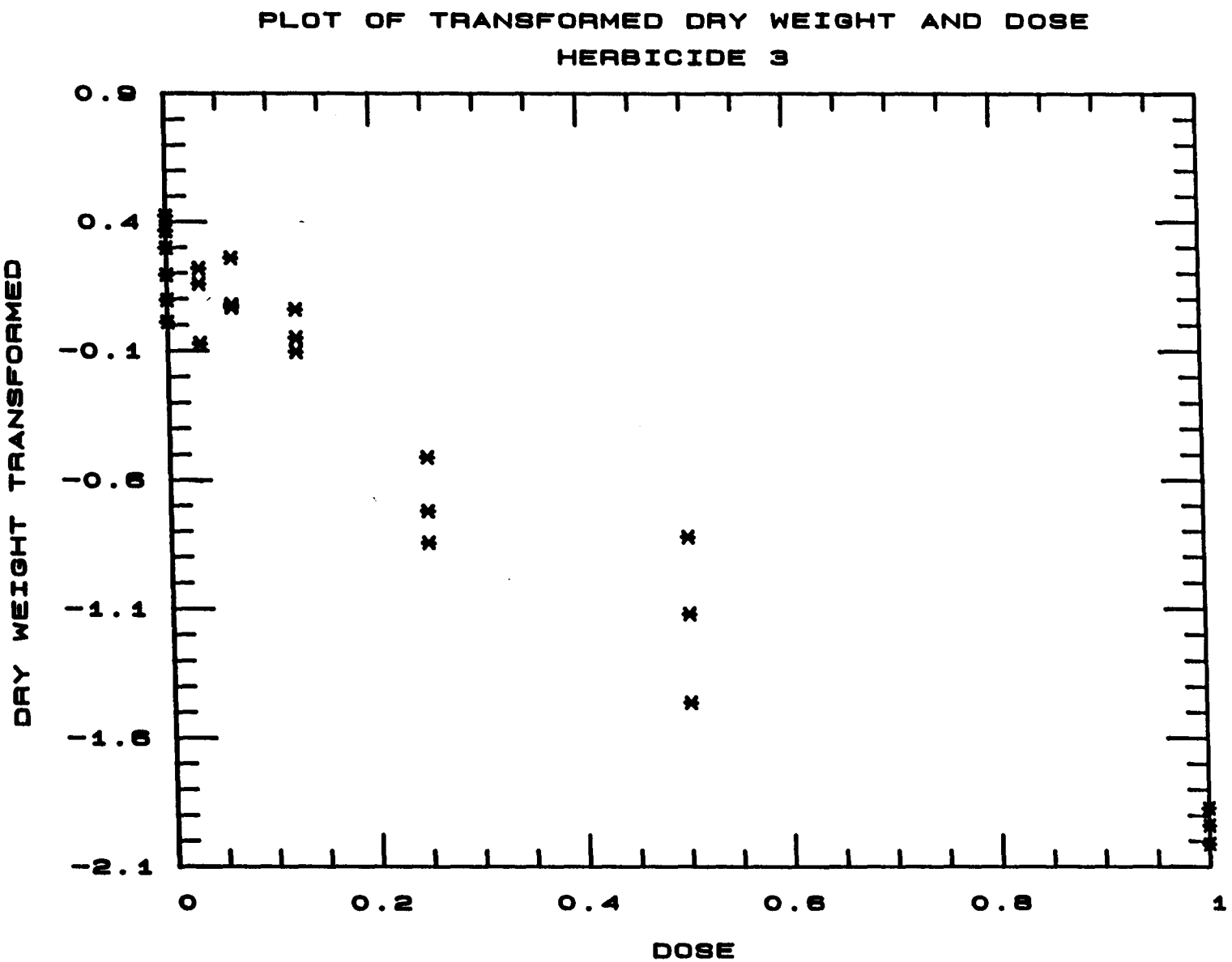

PLOT OF TRANSFORMED DRY WEIGHT AND DOSE
HERBICIDE 3
DRY WEIGHT TRANSFORMED
0.9
0.4
-0.1
-0.6
-1.1
-1.6
-2.1
0
0.2
0.4
0.6
0.8
1
DOSE

Fig 5

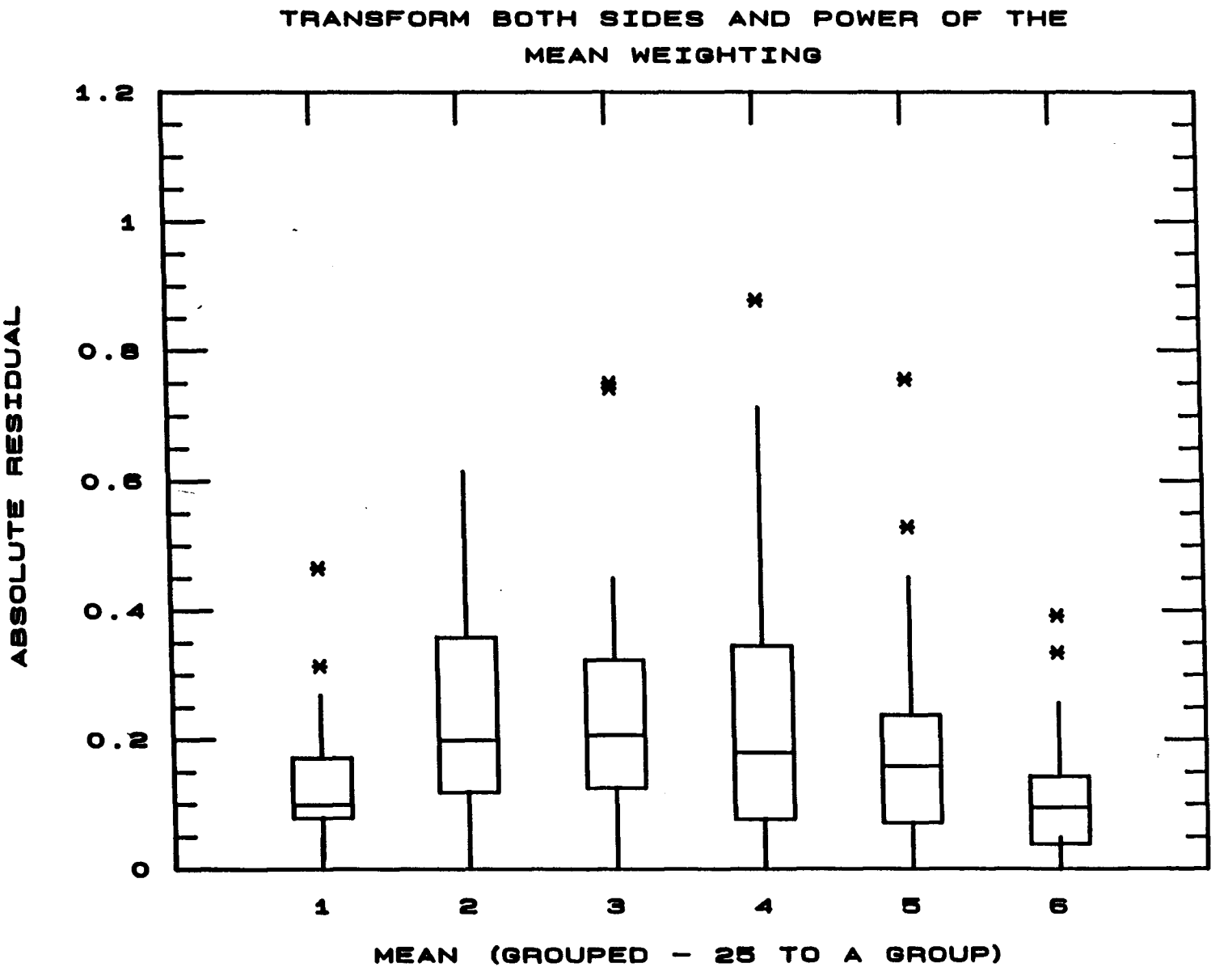

TRANSFORM BOTH SIDES AND POWER OF THE MEAN WEIGHTING
ABSOLUTE RESIDUAL
1.2
1
0.8
0.6
0.4
0.2
0
1
2
3
4
5
6
MEAN (GROUPED - 25 TO A GROUP)

Fig 6

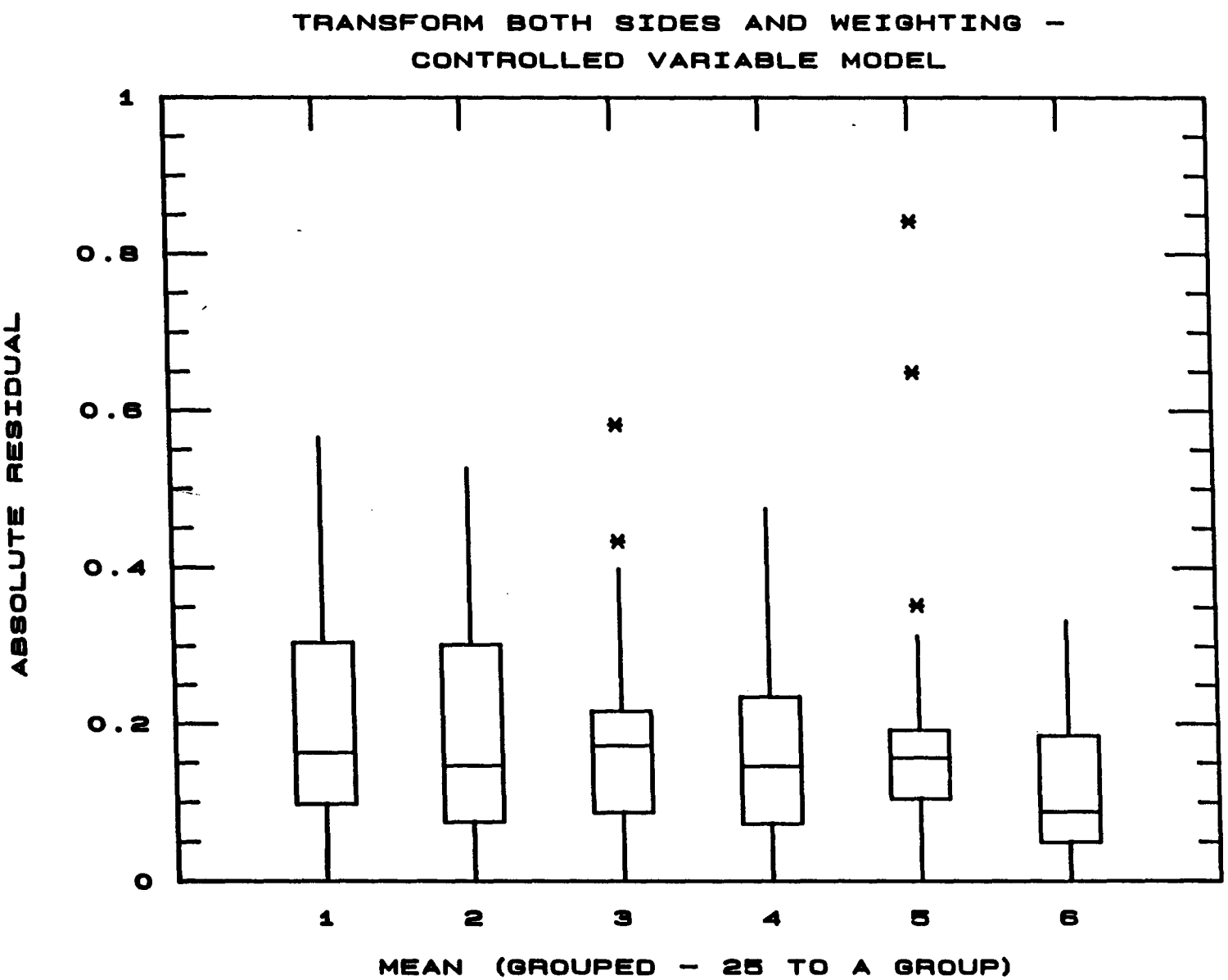
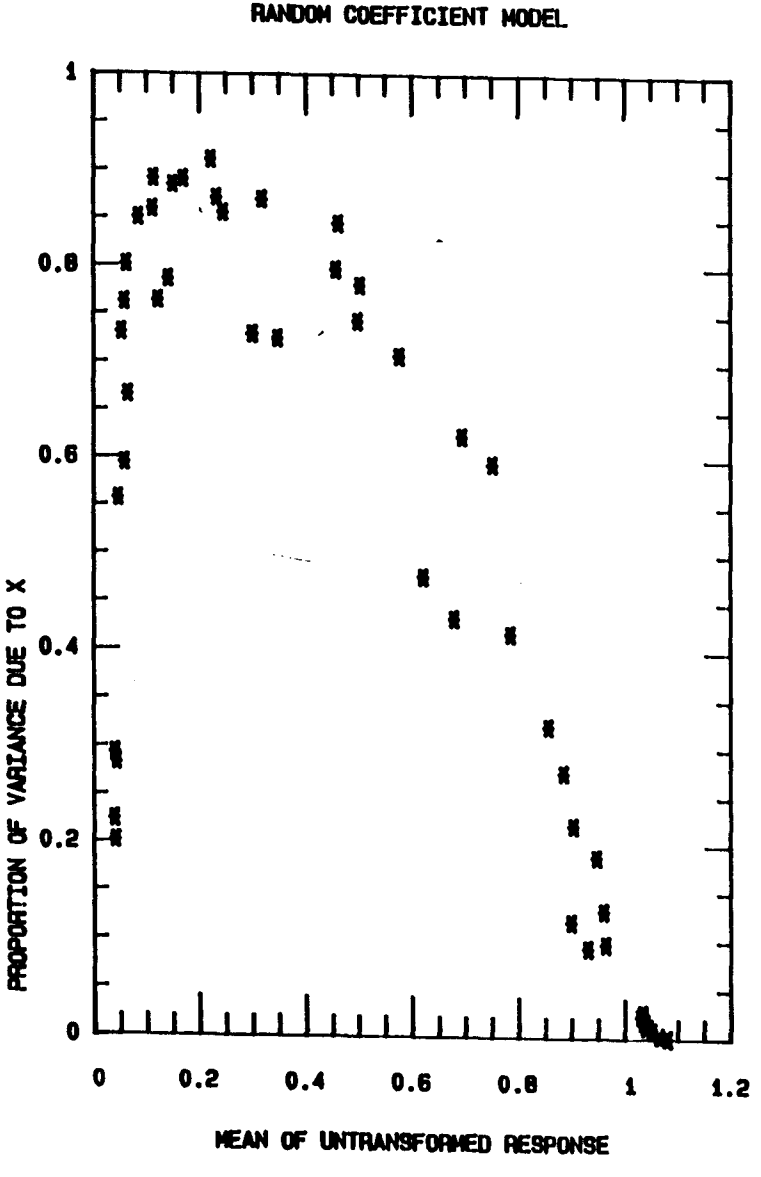
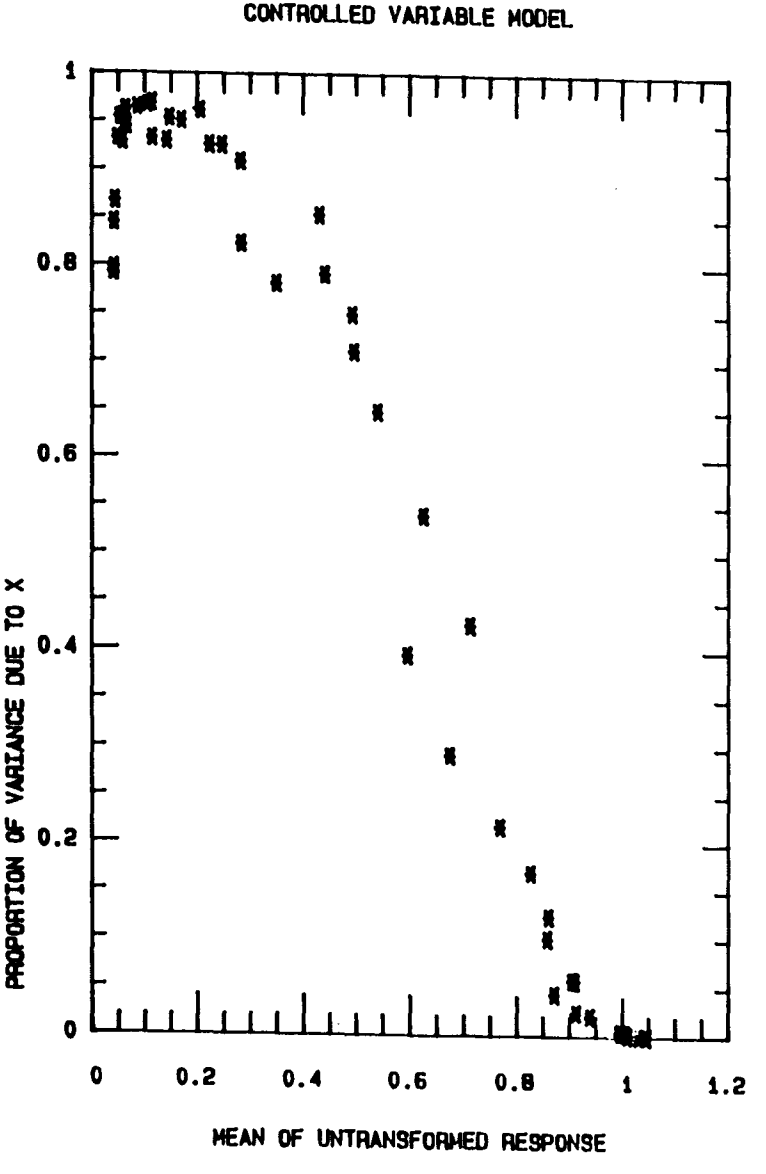

TRANSFORM BOTH SIDES AND WEIGHTING -
CONTROLLED VARIABLE MODEL
ABSOLUTE RESIDUAL
1
0.8
0.6
0.4
0.2
0
1
2
3
4
5
6
MEAN (GROUPED - 25 TO A GROUP)

Fig 7


RANDOM COEFFICIENT MODEL
PROPORTION OF VARIANCE DUE TO X
MEAN OF UNTRANSFORMED RESPONSE
0
0.2
0.4
0.6
0.8
1
1.2


CONTROLLED VARIABLE MODEL
PROPORTION OF VARIANCE DUE TO X
MEAN OF UNTRANSFORMED RESPONSE
0
0.2
0.4
0.6
0.8
1
1.2