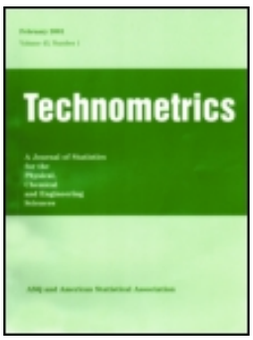

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The Experimental Study of Physical Mechanisms

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This paper is concerned with the dual problem of generating and analyzing data in experimental investigations in which the goal is to develop a suitable mechanistic model. The problem is first distinguished from that of response surface methodology. With regard to the analysis of data, topics that are discussed include the behavior of estimated constants with an inadequate model, a diagnostic technique for model-building, and the importance of visual scrutiny of data. With regard to the generation of data, the concept of placing a model in jeopardy is discussed. Designs for model discrimination and for parameter estimation are considered.

1. INTRODUCTION

1.1 *The General Problem*

The search for underlying physical mechanisms constitutes a major portion of effort in many scientific and engineering fields. To engineers, for example, basic mechanism studies are of interest principally because a deeper understanding makes it possible to cope with engineering design problems in a more successful manner than would be possible if the mechanism were entirely unknown.

Suppose that an experimenter is interested in studying a particular system for which there exists a mathematical model $\eta = f(\boldsymbol{\theta}, \boldsymbol{\xi})$, that is perhaps nonlinear in the parameters $\boldsymbol{\theta}$, which relates a measureable response η to the controllable variables $\boldsymbol{\xi}$. In a typical chemical engineering situation, for example, the response might be the rate of a chemical reaction, the variables might be partial pressures of the reactants and products, and the parameters might be adsorption equilibrium constants and an overall reaction rate constant. In practice, the quantities $\boldsymbol{\theta}$ are often referred to as constants rather than parameters.

The objective of the experimenter may be (1) to obtain an estimate of the response η over some particular region of interest in the space of the variables or (2) to determine the underlying physical mechanism of the phenomenon under investigation. Mathematically, we could say, for problem (2) the object is to discover the nature of the function $\eta = f(\boldsymbol{\theta}, \boldsymbol{\xi})$. In practical situations it is unlikely that we can ever know this completely. We shall say, however, that we have an adequate theoretical model when we have derived from a con-

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sideration of the mechanism a function which closely predicts the results of actual experiments.

In problem (1), which has come to be called the response surface problem, it is useful but not essential to employ such a theoretical model [7, 9, 11, 19]. In many circumstances even though no theoretical model is available, perfectly good empirical approximations can be obtained by fitting a polynomial or some other flexible graduating function over the region of interest [6, 12, 13, 14, 31, 34, 35, 36, 38]. Empirical models are, however, of limited value when the aim is to develop a suitable mechanistic theory. This paper is not concerned directly with problem (1) but rather with problem (2). Most statistical discussions begin by assuming that a model is known even though in practice, the model is usually unknown and the main problem is to build such a suitable model. The science of model-building has been a field neglected by most statistical authors. A notable exception, however, is the pioneering work of Cox on tests of separate families of hypotheses [21, 22].

1.2 *Cooperation between Experimenter and Statistician*

In model-building it is appropriate to speak of "tentatively entertaining" a given model rather than "assuming" it. This usage describes the attitude of the experimenter who suspects that a particular model may provide an adequate description of a system but bears in mind that the model may have to be modified or abandoned.

Data themselves cannot produce information; they can only produce information in the light of a particular model. But the model itself is not a fixed thing. Experimental results often show peculiarities which although meaningless to the statistician, might suggest to the experimenter a phenomenon other than that originally anticipated, that is, a change of model. To interpret the clues, therefore, one needs the cooperation of the expert in the subject matter field with the statistician. In some cases this is achieved by having the experimenter trained to act as his own statistician. A relevant example of the interplay between statistical analysis on the one hand and chemical engineering knowledge on the other is to be found in reference [28] where an appropriate model for the catalytic oxidation of methane was developed.

Here, then we are considering the problem of improving hypotheses iteratively, special emphasis being given to catalyzing the links between determining that a given model is inadequate, finding out *how* it is inadequate, and hence constructing a more appropriate model. The traditional statistical procedure of testing hypotheses has a more limited goal.

1.3 The Iterative Nature of *Experimentation*

The process of experimental investigation is an iterative one. In practice there may be backtracking, false starts, etc., but an underlying pattern can be seen. This involves the steps of conjecture (C), design (D), experiment (E), and analysis (A) continually repeated. As a result of some intuition, hypothesis, guess or *conjecture* the experimenter decides on a particular kind of plan or *design* of one or more experiments. These runs having been performed constitute

the *experiment* the data from which is mulled over from many points of view. This is the *analysis* which frequently leads to a modification of ideas. Then a new and perhaps somewhat more realistic conjecture is made which begins the iterative cycle over again. The adaptive sequence CDEACDEA . . . may be repeated many times before an investigation is complete.

Experimentation is thus essentially a dynamic process. Design leads to analysis via experiment and analysis leads to new design via conjecture. In parts 2 and 3 of this paper we will discuss design and analysis procedures developed in the context of this general framework.

2. Analysis of Data

Before discussing the generation of data we shall first consider three topics concerned with the analysis of data: (a) the behavior of estimated constants with an inadequate model, (b) a diagnostic technique for model-building, and (c) visual scrutiny of data. For a general account of statistical analysis of experimental data from mechanism studies the reader is referred to reference [9].

2.1 *Behavior* of *Estimated Constants with an Inadequate Model*

In the physical and biological sciences a mechanistic model is often expressed most naturally in terms of one or more time- or space-dependent differential equations. For example, we may describe some phenomenon by the time-dependent differential equation

$$\frac{d\eta}{dt} = \phi(\boldsymbol{\theta}; \eta, \boldsymbol{\xi}, t) \tag{1}$$

subject to certain boundary conditions. Upon integration this equation may yield

$$\eta = f(\boldsymbol{\theta}; \boldsymbol{\xi}, t) \tag{2}$$

In conducting experiments on such a system it is usually most convenient to set the variables $\boldsymbol{\xi}$ at some fixed set of values and make a "run" in which observations are made at m specified values of t; the values of $\boldsymbol{\xi}$ are then reset and a second run is made in which observations are taken once again at the same values of t; and so on. Let y_{ui} denote the i-th observation of the u-th run. Suppose that the method of least squares is appropriate and we can obtain a set of such estimates

$$\hat{\boldsymbol{\theta}}_u' = (\hat{\theta}_{1u}, \hat{\theta}_{2u}, \cdots, \hat{\theta}_{pu}) \tag{3}$$

for the p parameters from the m observations $y_{u1}, y_{u2}, \ldots y_{um}$ in *the u-th run.* Suppose that n runs and N = nm observations are made in all.

By fitting *the complete set* of *data* suppose we obtain least squares estimates

$$\hat{\boldsymbol{\theta}}' = (\hat{\theta}_1, \hat{\theta}_2, \cdots, \hat{\theta}_p). \tag{4}$$

We show in Appendix A how specific inadequacies of the model may be detected by studying the dependence of the discrepancies $\hat{\boldsymbol{\theta}}_u - \hat{\boldsymbol{\theta}}$ on the levels $\boldsymbol{\zeta}_u$ of the variables.

2.2 *A Diagnostic Technique for Model-Building*

In any least squares analysis, of course, it is possible to check the lack of fit by examining the residuals and, in particular, the residual sum of squares. The object of our analysis, however, is not only to establish whether there is lack of fit but, if so, to provide some indication of its nature and so to help the experimenter decide how to modify the model.

As we have stated in the previous section, when the model is inadequate the within-run least squares estimates $\hat{\boldsymbol{\theta}}_u$ may vary as the levels of the experimental variables are changed. In order to diagnose the source of lack of fit it is important to obtain accurate information concerning which $\hat{\theta}$'s are dependent on which ξ's. To allow best estimation and separation of such effects it is useful to run a formal design such as a factorial in the f's.

In the simplest application of this technique, if there were no experimental error and the model were adequate, then all the estimates $\hat{\boldsymbol{\theta}}_u$ would be equal, i.e., constant from run to run. We can, therefore, proceed as follows. First, the adequacy of the model with respect to each individual run is checked by examining residuals within runs. Then a statistical analysis is applied to the estimated quantities $\hat{\boldsymbol{\theta}}_u$ to see whether there is any evidence that they are related to the level of the ξ's.

If a factorial design is employed such an analysis is particularly easy. The usual main effects and interactions are calculated treating the estimated parameters as observations. The existence of non-zero main effects and interactions would indicate via the above results the need for modification.

In other than the simplest applications, rather than no effect being expected it may be that an effect of a specific type would be expected from a particular model. For example, when an Arrhenius type model was used the logarithm of the rate constant would be expected to be linearly related to the reciprocal of the absolute temperature. Thus, a main effect would be expected in the analysis of the estimated parameter corresponding to temperature (it would, in fact, be related to the activation energy) but there would be no interaction effects with, for example, the concentrations of the reactants. This diagnostic technique for model-building has been discussed in references [15] and [28] and will here be illustrated with an example taken from the second of these references.

An Example

The catalytic oxidation of methane

$$CH_4 + 2O_2 \xrightarrow[\text{catalyst}]{} CO_2 + 2H_2O$$

was investigated. At one stage the mechanism entertained was that gaseous methane and adsorbed oxygen react on the catalyst surface to produce gaseous carbon dioxide and adsorbed water. On the assumption that oxygen is adsorbed on adjacent dual sites the following mathematical model was appropriate

$$t = \int_0^{\eta} \frac{(\theta + \theta'\eta)^2}{\xi_1(1 - \eta)(\xi_2 - 2\xi_1\eta)^2}\, d\eta \qquad (6)$$

where

$$\theta = \beta_0 + \beta_2\xi_2 + \beta_3\xi_3$$
$$\theta' = (\beta_3 - 2\beta_2)\xi_1 \tag{7}$$

and

$$\beta_0 = \frac{1}{\sqrt{kK_1}}$$
$$\beta_2 = \frac{1}{\sqrt{k}}$$
$$\beta_3 = \frac{K_2}{\sqrt{kK_1}}$$

with

t = (weight of catalyst)/(mass flow of gas)
ξ_1 = mole fraction of methane
ξ_2 = mole fraction of oxygen
ξ_3 = mole fraction of carbon dioxide
η = fractional conversion of methane
k = overall surface reaction rate constant
K_1 = adsorption equilibrium constant for oxygen
K_2 = adsorption equilibrium constant for carbon dioxide

It will be noted that the variable ξ_4, the mole fraction of water vapor, does not appear in model 6 at all, although this could be an important factor if certain plausible rival mechanisms were appropriate. This model, then, implies in particular that the parameter θ, although linearly related to the variables ξ_2 and ξ_3, should be unrelated to the variables ξ_1 and ξ_4. A 2^{4-1} fractional factorial design run in the variables ξ_1, ξ_2, ξ_3, and ξ_4 allowed us to discover experimentally with which of the variables the parameter θ was related. For each of the 8 sets of factor combinations of the design, observations of η were made at three distinct level of t.

It was necessary to realign the apparatus when the variable t was changed as well as when the variables ξ_1, ξ_2, ξ_3, and ξ_4 were changed so that for this investigation the 24 distinct experiments could without inconvenience be made completely randomly in time order. From these 24 experiments, eight η vs. t curves could be fitted from which eight individual estimates $\hat{\theta}_u$ could be readily obtained. Furthermore, a reasonably reliable estimate of experimental error could be obtained from the deviations from the fitted curves.

It is now a simple matter to fit

$$\tilde{\theta} = \hat{\beta}_0 + \hat{\beta}_2\xi_2 + \hat{\beta}_3\xi_3$$

which if the model were adequate, would completely account for the variation in $\hat{\theta}$. In this expression $\hat{\beta}_0$ would simply bc the average of thc $\hat{\theta}$'s while $\hat{\beta}_2$ and $\hat{\beta}_3$ would be one half of the "main effects" associated with ξ_2 and ξ_3. Our model implies that only these "effects" ought to be found. In particular there should

be no "effects" associated with ξ_1 or ξ_4 and no interactions of any kind. In fact, the discrepancies $\hat{\theta} - \tilde{\theta}$ shown in Table 1 indicate when experimental error is taken into account that this is not the case and hence that the model is inadequate.

It will be noticed that the signs of $\hat{\theta} - \tilde{\theta}$ are perfectly correlated with the signs of variable ξ_4, water vapor. This particular model, then, does not take the concentration of water vapor properly into account. Since it had at the beginning of this stage been supposed that the reaction yields non-adsorbed water vapor, a modified model which considers adsorbed water vapor was a logical next step. After further analysis it was shown that a model of this kind was indeed adequate.

TABLE 1

Intermediate Analysis of Data from Study on the Catalytic Oxidation of Methane.

Run	Design				Discrepancies
	ξ_1	ξ_2	ξ_3	ξ_4	$(\hat{\theta}_u - \tilde{\theta}_u) \times 10^4$
1	- 1	- 1	- 1	+1	+3.63
2	$ 1	- 1	- 1	- 1	-2.88
3	−1	$ 1	- 1	- 1	-6.68
4	$1	$1	-1	+1	$5.28
5	- 1	- 1	+1	- 1	-5.13
6	+1	-1	+1	+1	+4.07
7	-1	+1	+1	+1	+6.27
8	+1	+1	+1	-1	-4.56

2.3 *Visual Scrutiny* of *Data*

The value of graphs and diagrams cannot be overemphasized. It has been our experience that research workers do not exploit visual devices as much as they should. We summarize here some of the more important kinds of graphs and diagrams that have been found helpful.

Residuals

The residuals are defined as the discrepancies

$$y_j - \hat{y}_j \qquad (j = 1, 2, \cdots, N)$$

where

y_j = observed value of response
$\hat{y}_j$ = fitted value of response.

If the model is adequate the residuals will be manifestations of completely random variation apart from restrictions imposed by the analysis. An example of this kind of restriction is that the sum of the residuals from an arithmetic average always equals zero.

All the information relating to the possible inadequacy of a tentatively entertained model is contained in the residuals. Plots of residuals, therefore, can reveal particular aspects of the model that should be improved. Consequently, as a matter of course, residuals should always be plotted in any way that might shed light on pertinent questions [2, 9]. To list some examples, the residuals might be plotted against (1) the time order in which the experiments were performed, (2) the level of each of the variables, and (3) the predicted value of the response. (Two plots illustrating case (3) arc presented in Anseombe [2]). The question being asked in each case might be (1) Is there a time trend in the results? (2) Does the model fail to take any of the variables properly into account? Is there evidence of a quadratic trend? (3) Does the variability increase as the magnitude of the predicted value of the response increases? Is there a quadratic dependence between the residuals and the predicted values of the response suggesting lack of fit which can be cured by transforming y? [19A]

Dot diagrams or (if enough observations are available) histograms can be constructed to check on the distribution of the residuals to see if it has any unusual characteristics. If there is one residual that is much larger in magnitude than the others, for example, it will deserve further attention. There may have been a mistake in carrying out that particular experiment (e.g., the wrong reagent was used, the variables were set at grossly incorrect levels, or the measuring instrument was out of calibration) or there may have been a copying or an arithmetic error. On the basis of a careful check for blunders of this kind the response for that run may be accepted as is, corrected, or rejected. The literature on outliers is relevant here. (See [1], [23], [26], [27], [31], [32], [40], and the references listed therein).

Perhaps no blunder has occurred but rather the apparently anomalous observation can be explained in some other way, e.g., by a mechanism other than the one currently being considered. The value of a single observation in this way can sometimes be greater than all the other observations in model-building situations because it leads the experimenter to new and valuable conjectures.

Contour Diagrams

Plotting contour diagrams can also be helpful in summarizing the main features of a model. In such diagrams limes (or surfaces) of constant response levels are plotted as functions of the experimental variables. Contour diagrams are often useful when more than one response is of importance. In such cases the individual diagrams can be overlaid. Examples of plots showing more than one response are contained in references [34], [35], [36], and [38].

Likelihood Function

Diagrams can also be extremely helpful in gaining a better understanding of the estimation situation. Point estimates of parameters are unsatisfactory without some indication of their precision. One effective way of displaying this information is to plot the likelihood function, as was advocated by Fisher and later reemphasized by Barnard, Jenkins and Winsten [3] and Box [9].

If the errors are normally and independently distributed with constant

variance σ^2 the log likelihood $l(\boldsymbol{\theta})$ is simply a linear function of the sum of squares $S(\boldsymbol{\theta})$. That is, with m observations,

$$l(\boldsymbol{\theta}) = -\frac{m}{2} \ln 2\pi\sigma^2 - \frac{1}{2\sigma^2} S(\boldsymbol{\theta})$$

where

$$S(\boldsymbol{\theta}) = \sum_{i=1}^{m} \{y_i - f(\boldsymbol{\theta}, \xi_i)\}^2$$

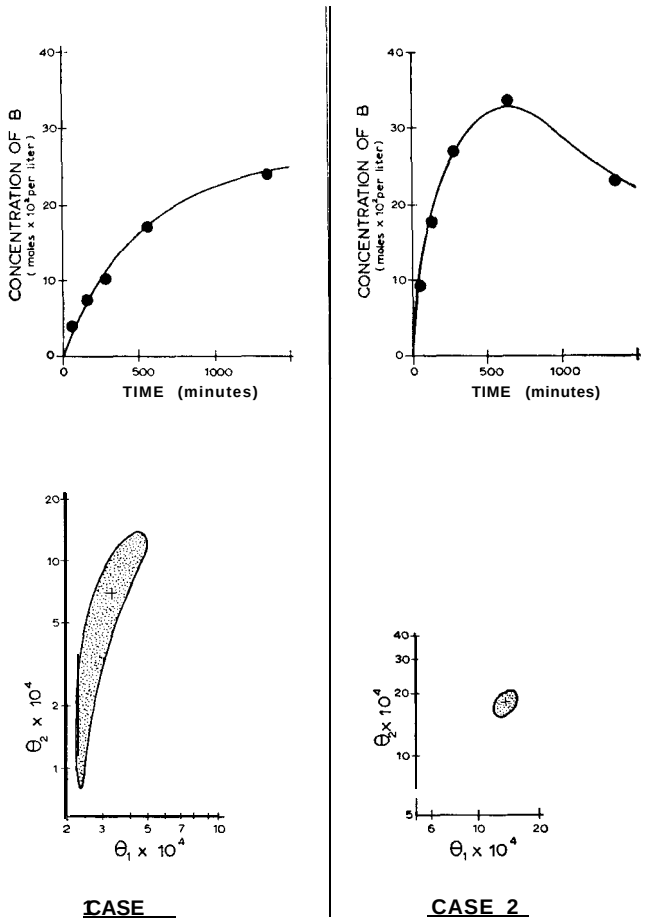

FIGURE 1

Typical Fitted Curves and Corresponding Approximate 95% Confidence Regions for Two Different Situations

Therefore, if there are only two or three parameters a contour diagram of the likelihood (or, equivalently, the sum of squares) function can be readily produced.

For example, suppose that chemical reaction of the type $A \rightarrow B \rightarrow C$ were being studied and the concentration of [B] were measured at five different

times t. The models being entertained might be of the form

$$\eta = \frac{[A]_0\theta_1}{\theta_1 - \theta_2}(e^{-\theta_2 t} - e^{-\theta_1 t})$$

where

η = concentration of B at time t
$[A]_0$ = initial concentration of A

and θ_1 and θ_2 are first order rate constants to be estimated. Figure 1 shows typical runs that might have been made with two different reactions of this kind. (These are, in fact, runs 1 and 13 in reference [15].)

The contours shown are those for which the sum of squares $\sum_{i=1}^{5}(y_{ui} - \eta_{ui})^2$, considered as a function of θ_1 and θ_2, is equal to the constant

$$S_{\min} + s^2 pF_{0.05}(2,48)$$

where

S_{min} = minimum value of the sum of squares $S(\boldsymbol{\theta})$
s^2 = an estimate of the within run variance associated, in this example, with 48 degrees of freedom
p = 2, the number of parameters estimated
$F_{0.05}(2,48)$ = the usual 5% value of the F criterion with 2 and 48 degrees of freedom.

If the model were linear the regions so defined would be 95% confidence regions, or, under suitable assumptions, 95% Bayesian regions, (see Appendix B).

These contours agree with common sense. They clearly show, for example, that if data are taken only over the early part of such a curve, relatively imprecise and highly correlated estimates are obtained, whereas if the data "cover" the major features of the curve, markedly better estimates can be obtained. Many choices of the parameters which can match the beginning part of the curve are eliminated when more of the curve is covered by experimental runs. This is a simple example which clearly illustrates the importance of good design in obtaining reliable estimates of parameters.

This graphical approach can be extended to three or four parameters by exhibiting a "grid" of two-dimensional (θ_1, θ_2) plots for various combinations of θ_3 and θ_4. An instrument such as the "Calcomp" plotter can produce such plots automatically from digital computer output and such plotting should be part of the normal stock in trade of the practicing statistician. The technique immediately shows up peculiarities of an estimation situation (for example: non-stationary maxima on a boundary of the permissible parameter space and excessive non-linearity evidenced by non-elliptic contours). When each of several responses contribute information about a particular set of parameters overlaid plots of this kind are particularly valuable [19B].

3. DESIGN OF EXPERIMENTS

Of the two, design and analysis, the former is undoubtedly of greater importance. The damage of poor design is irreparable; no matter how ingenious the

analysis, little information can be salvaged from poorly planned data. On the other hand, if the design is sound, then even quick and dirty methods of analysis can yield a great deal of information. For further discussion of this point see [8].

3.1 *Placing a Model in Jeopardy*

In many instances the experimental design is such that even when serious inadequacies exist they are undetectable. Yates [42] was referring to this fact when he stated that "nothing is easier than to 'prove' that a hypothesis is true by testing it by an experiment which is sufficiently inaccurate". It should be understood that the difficulty here is not merely associated with possible inaccuracy in the observations. Even with fairly accurate observations experiments can be of such a type that they are insensitive to departures from the model. Although they do not disprove a particular model they do not disprove a vast number of other models either.

For example, suppose a model represents the concentration η of a chemical product as a function of time t and a number of parameters $\theta' = (\theta_1, \theta_2, \cdots 0,)$. Suppose that $\eta = 0$ at time $t = 0$. If observations are made only for small values of t over which period the curve starting from the origin is roughly a straight line, then clearly it could represent the beginning of almost any kind of reaction. Undoubtedly, values of the θ's can be found which will fit the data with this particular type of model but this would be true for many other models as well. Specifically, the model being fitted could be wrong and yet this fact could go unrecognized because of the nature of the experimental design. In such a case we shall say that the experimental design has been such as to never *place the model in jeopardy*. The common practice in kinetic studies of analysing only initial rates of chemical reaction is particularly vulnerable to this criticism.

3.2 Designs for Model Discrimination

Suppose that an experimenter is studying a chemical reaction in which a reactant A is used to make a product B. Simultaneously, however, an undesired by-product C is formed. Suppose further that the experimenter knows that the reaction is one of the following:

Mechanism 1: $A \rightarrow B \rightarrow C$
Mechanism 2: $A \rightarrow B \rightleftarrows C$

Typical curves showing the concentration of the product B as a function of time are shown in Figure 2. If one of these mechanisms is actually correct and all experiments consist of measurements of the concentration of B at times less than 10 minutes, then obviously it will be virtually impossible to distinguish between Mechanism 1 and 2. Observations are needed at times of the order of 100 minutes.

Where to place experiments to discriminate most efficiently between two models will depend in general on the values of the estimated parameters. A sequential scheme, therefore, suggests itself in which at each stage the two models are refitted and a decision is made as to what experiment should be run next. The feasibility of such an iterative procedure is presently under investigation.[28A]

3.3 *Designs* for *Parameter Estimation*

If the form of the theoretical model is known, the problem which confronts the experimenter is to evaluate the physical parameters (e.g., rate constants in chemical kinetics examples). In this section, we consider the problem of the generation of data in this situation.

If experiments are not carefully planned the experimental points may be so situated in the space of the variables that the estimates which can be obtained for the parameters $\boldsymbol{\theta}$ are not only imprecise but also highly correlated. Once the data are collected a statistical analysis, no matter how elaborate, can do nothing to remedy this unfortunate situation. However, by selecting a suitable experimental design in advance these shortcomings can often be overcome. Although the problem of designing experiments in non-linear situations has received comparatively little attention, some possible approaches have been suggested. See, for example, references [17], [20], [25], [29], [30], [39] and [41]. Blakemore and Hoer1 [5] made a rather strong appeal for further work in this important area.

Box and Lucas [17], whose approach has since been applied, for example, to chemical problems by Behnken [4], proceeded by attempting to choose a design D in such a manner that the volume of the approximate confidence region for $\boldsymbol{\theta}$ is minimized, or, equivalently, under suitable assumptions, trying to choose D to minimize the volume in the parameter space which contains a given percentage of the posterior distribution. If the experimental errors are approximately Normally distributed and the response relationship is approximately linear in the vicinity of the least squares estimates $\hat{\boldsymbol{\theta}}$, then the volume of this region is proportional to the square root of the reciprocal of the determinant $A = X'X$ where $X = \{x_{ru}\}$ and

$$x_{ru} = \left\{\frac{\partial f(\boldsymbol{\theta},}{\mathrm{d}e,}\right\}_{\boldsymbol{\theta}=\hat{\boldsymbol{\theta}}}$$

Unfortunately, since we do not know the values of $\hat{\boldsymbol{\theta}}$ in advance, we do not know the derivatives x_{ru} on which the design is to be based. In most cases, however, some knowledge of the size of the parameters will be available and it was suggested [IT] that preliminary guesses $\boldsymbol{\theta}^0$ should be made, and that the derivatives should be determined at these values $\boldsymbol{\theta}^0$ instead of $\hat{\boldsymbol{\theta}}$. The resulting determinant $\Delta^0 = X^{0\prime}X^0$ is an explicit function of the settings of the experimental variables ξ. It is therefore possible to find (perhaps analytically but, in any event, numerically) those values for ξ which maximize the determinant Δ^0.

At first sight it may seem strange that in order to use this scheme one must initially have estimates of the parameters since, after all, it is the purpose of the experiment to obtain such estimates. Actually, however, this is merely an example of the fact that any experimental design uses the experimenter's beliefs about the situation being studied. It is thus efficient depending on whether the experimenter turns out to be nearly right. In general, the more one knows initially the better he can design experiments. As has been pointed out previously [9], if nothing is known about the experimental situation then strictly speaking no experiment can be planned.

Since the best design depends upon the parameters that are to be estimated,

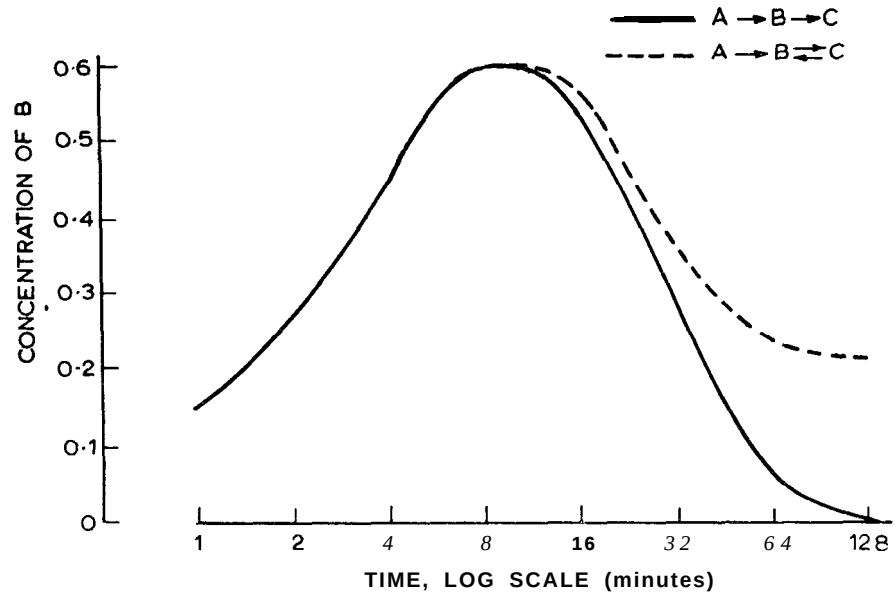

FIGURE 2

Two Curves Representing the Concentration of B as a Function of Reaction Time for the Two Mechanisms $A \rightarrow B \rightarrow C$ and $A \rightarrow B \rightleftarrows C$

it was suggested [16] that a sequential plan be employed in which at each stage the parameters be reestimated. With these current estimates a calculation would be made to determine where the next experiment should be run. The feasibility of this method was dcmonstratcd with an example based on the catalytic dehydration of n-hexyl alcohol [33], the model being

$$\eta = \frac{\theta_3 \theta_1 \xi_1}{1 + \theta_1 \xi_1 + \theta_2 \xi_2}$$

where

η = true rate of reaction
θ_1 = adsorption equilibrium constant for alcohol
θ_2 = adsorption equilibrium constant for olefin
θ_3 = effective reaction rate constant
ξ_1 = partial pressure of alcohol
ξ_2 = partial pressure of olefin

Data were constructed on the assumption that the true parameter values were

$$\theta_1 = 2.9 \qquad \theta_2 = 12.2 \qquad \theta_3 = 0.60$$

and that

$$y = \eta + \epsilon$$

where

y = observed rate of reaction
η = true rate of reaction
ϵ = error

The error ϵ was taken to be Normally and independently distributed with zero mean and standard deviation $\sigma = 0.01$. It was further supposed that neither partial pressure could be set greater than three atmospheres so that the experimental region was that shown in Figure 3.

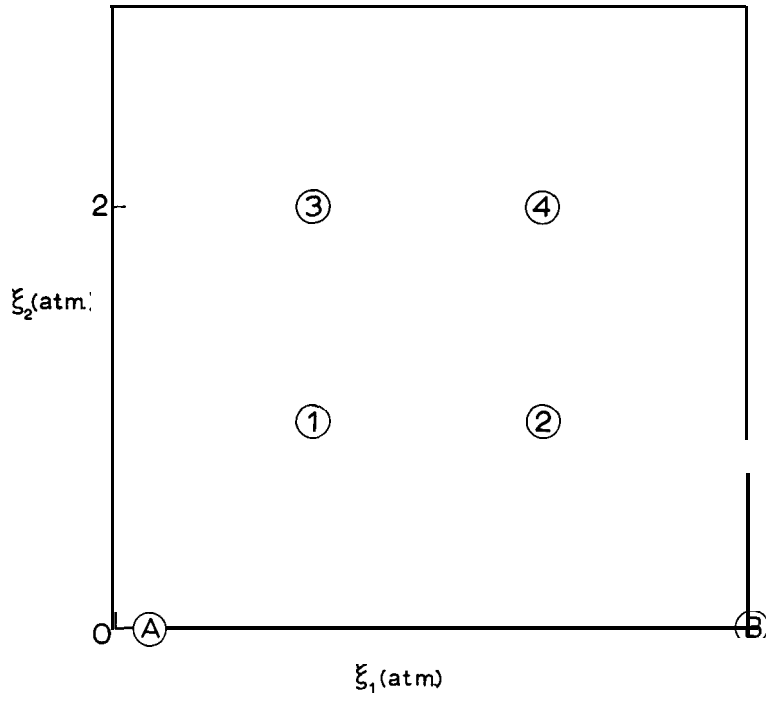

FIGURE 3

Location of Experimental Points in the Factor Space for a Sequentially Designed Set of Runs for the Model $\eta = \theta_3\theta_1\xi_1/(1 + \theta_1\xi_1 + \theta_2\xi_2)$

An initial set of four experiments was "run" according to a standard 2^2 factorial pattern. These runs are indicated by the circled numbers 1, 2, 3 and 4 in the figure. At each successive stage thereafter, the experimenter supplied a digital computer with (a) the model, (b) the data, and (c) the current least squares estimates of the parameters of the model; and the computer in turn produced (a) the new least squares estimates, (b) the value of the determinant criterion as a function of various choices of contemplated settings of the variables, and (c) the experimental conditions for the next experiment which maximized the determinantal criterion. The next nine runs fell near the three areas denoted by circled letters A, B, and C in the following order:

ABABACBAC

The procedure can be modified by considering, for example, special information about the dispersion matrix.

4. Conclusion

This paper has been concerned with some statistical aspects of the dual problem of generating and analyzing data in experimental investigations in which the goal is to develop or build a suitable mechanistic model. Such investigations consist logically of two steps: (i) establishing the form of an adequate model and then (ii) estimating precisely the values of its parameters. Fisher, incidentally, referred to these as the problems of (i) specification and (ii) estimation. For the first step one of the methods mentioned for placing the model in jeopardy might be used, and for the second step one of the suggestions discussed in Section 3.3 might be used. The aim of the first type of design would be, by straining a tentative model, to iterate towards a satisfactory formulation, and the aim of the second type would be to obtain improved estimates of the parameters once a suitable form of the function is established.

There may be better methods, however, for dealing with this two-part problem. One might suppose that a class of sequential designs could exist which would permit an attack on both problems from the outset of the investigation and would facilitate the transition from step (i) to (ii).

5. Appendix A

Behavior of Estimated Constants with an Inadequate Model

The general setup is that given in Section 2.1. Recall that the estimates of the parameters from the observations $y_{u1}, y_{u2}, \ldots, y_{um}$ in *the u-th* run are denoted by $\hat{\boldsymbol{\theta}}_u$ and the estimates obtained from fitting *the complete set* of *data* are denoted by $\hat{\boldsymbol{\theta}}$. Suppose that

$$r_{ui} = y_{ui} - f(\boldsymbol{\theta}^0; \xi_u, t_i) \quad \begin{matrix} u=1,2,\cdots,n \\ i=1,2,\cdots,m \end{matrix} \tag{A-1}$$

where $\boldsymbol{\theta}^0$ is some convenient point in the parameter space in the neighborhood of the point representing estimates and that

$$x_{ui}^{(j)} = \left[\frac{\partial f(\boldsymbol{\theta}; \xi_u, t_i)}{\partial \theta_j}\right]_{\boldsymbol{\theta}=\boldsymbol{\theta}^0} \tag{A-2}$$

Then if linear approximation suffices over the relevant region our model may be written

$$E(r_{ui}) = \sum_{j=1}^{p} (\theta_j - \theta_j^0) x_{ui}^{(j)}. \tag{A-3}$$

All the information on the adequacy of the model is contained in the N residuals whose sum of square is

$$S_R = \sum_{u=1}^{n} \sum_{i=1}^{m} \left\{ r_{ui} - \sum_{j=1}^{p} (\hat{\theta}_j - \theta_j^0) x_{ui}^{(j)} \right\}^2 \tag{A-4}$$

which is associated with N-p degrees of freedom.

Decomposition of *the* Residuals

Now

$$S_R = \sum_{u=1}^{n}\sum_{i=1}^{m}\left\{\left[r_{ui} - \sum_{j=1}^{p}(\hat{\theta}_{ju} - \theta_j^0)x_{ui}^{(j)}\right] - \left[\sum_{l=1}^{p}(\hat{\theta}_l - \hat{\theta}_{lu})x_{ui}^{(l)}\right]\right\}^2 \quad \text{(A-5)}$$

$$= \sum_{u=1}^{n}\sum_{i=1}^{m}\left\{r_{ui} - \sum_{j=1}^{p}(\hat{\theta}_{ju} - \theta_j^0)x_{ui}^{(j)}\right\}^2 + \sum_{u=1}^{n}\sum_{j=1}^{p}\sum_{l=1}^{p}(\hat{\theta}_j - \hat{\theta}_{ju})(\hat{\theta}_l - \hat{\theta}_{lu})c_{ujl} \quad \text{(A-6)}$$

where

$$c_{ujl} = \sum_{i=1}^{m} x_{ui}^{(j)} x_{ui}^{(l)}$$

since

$$\sum_{u=1}^{n}\sum_{l=1}^{p}(\hat{\theta}_l - \hat{\theta}_{lu})\sum_{i=1}^{m}\left\{r_{ui} - \sum_{j=1}^{p}(\hat{\theta}_{ju} - \theta_j^0)x_{ui}^{(j)}\right\}x_{ui}^{(l)} = 0 \quad \text{(A-7)}$$

The residual sum of squares may thus be decomposed into two parts S_W and S_B which add to give S_R. The within-run residual sum of squares S_W is

$$S_W = \sum_{u=1}^{n}\left\{\sum_{i=1}^{m} r_{ui} - \sum_{j=1}^{p}(\hat{\theta}_{ju} - \theta_j^0)x_{ui}^{(j)}\right\} \quad \text{(A-8)}$$

This, in turn, can be split into n separate sums of squares associated with the n separate runs. The u-th such sum of squares is

$$S_{Wu} = \sum_{i=1}^{m}\left\{r_{ui} - \sum_{j=1}^{p}(\hat{\theta}_{ju} - \theta_j^0)^2 x_{ui}^{(j)}\right\}^2 \quad \text{(A-9)}$$

Lack of fit in the u-th run will be indicated by an inflation of this sum of squares. The between run sum of squares is

$$S_B = \sum_{u=1}^{n}\sum_{j=1}^{p}\sum_{l=1}^{p}(\hat{\theta}_{ju} - \hat{\theta}_j)(\hat{\theta}_{lu} - \hat{\theta}_l)c_{ujl} \quad \text{(A-10)}$$

We notice that this second quadratic form focuses attention on the changes in the estimates of the θ's which occur from run to run, that is to say as the levels of the variables are changed.

Model Adequate

Let the m $\times$ p matrix of the derivatives $x_{ui}^{(j)}$ in the u-th run be denoted by X_u and the corresponding m $\times$ 1 vector of the elements $r_{u1}, r_{u2}, \cdots, r_{um}$ by r_u. Then

$$(\hat{\boldsymbol{\theta}}_u - \boldsymbol{\theta}^0) = (X_u'X_u)^{-1}X_u'r_u \quad \text{(A-l 1)}$$

Now the expected values of these estimates are

$$E(\hat{\boldsymbol{\theta}}_u - \boldsymbol{\theta}^0) = (X_u'X_u)^{-1}X_u'E(r_u) \quad \text{(A-12)}$$

and if the model is adequate

$$E(r_u) = X_u(\boldsymbol{\theta} - \boldsymbol{\theta}^0) \quad \text{(A-13)}$$

whence

$$E(\hat{\boldsymbol{\theta}}_u - \boldsymbol{\theta}^0) = \boldsymbol{\theta} - \boldsymbol{\theta}^0. \tag{A-14}$$

Thus on our assumptions the estimates 6, are unbiassed estimates of $\boldsymbol{\theta}$ and in particular they do not depend on the levels of the variables $\boldsymbol{\xi}$.

Model Inadequate

Now suppose that the true form of the function is not $\eta = f(\boldsymbol{\theta}; \boldsymbol{\xi}, t)$ but

$$\eta = \zeta(\boldsymbol{\psi}; \boldsymbol{\xi}, t) \tag{A-15}$$

Then

$$E(\hat{\boldsymbol{\theta}}_u - 8") = (X_u'X_u)^{-1}X_u'\Delta_u \qquad u = 1, 2, \cdots, n \tag{A-16}$$

where the i-th element of the $m \times 1$ vector Δ_u is

$$\zeta(\boldsymbol{\psi}; \boldsymbol{\xi}_u, t_i) - f(\boldsymbol{\theta}^0; \boldsymbol{\xi}_u, t_i) = \Delta(\boldsymbol{\psi}, \boldsymbol{\theta}^0; \boldsymbol{\xi}_u, t_i) \tag{A-17}$$

We note that now the elements in X_u and in Δ_u on the right hand side of Equation A-16 all depend on $\boldsymbol{\xi}$.

Specifically, suppose we choose a particular central point $\boldsymbol{\xi}^0$ in the space of the variables about which the levels $\boldsymbol{\xi}_u$ vary in successive experiments. Then expanding about this value we can write

$$X_u = \left[\frac{\partial f(\boldsymbol{\theta}; \boldsymbol{\xi}_u, t_i)}{\partial \theta_j}\right]_{\boldsymbol{\theta}=\boldsymbol{\theta}^0} \doteq A + \sum_{h=1}^{k} (\xi_{hu} - \xi_h^0)B_h \quad \begin{matrix} i = 1, 2, \cdots, m \\ j = 1, 2, \cdots, p \\ u = 1, 2, \cdots, n \end{matrix} \tag{A-18}$$

where

$$A = \left[\frac{\partial f(\boldsymbol{\theta}; \boldsymbol{\xi}, t_i)}{\partial \theta_j}\right]_{\substack{\boldsymbol{\theta}=\boldsymbol{\theta}^0 \\ \boldsymbol{\xi}=\boldsymbol{\xi}^0}} \tag{A-19}$$

$$B_h = \left[\frac{\partial^2 f(\boldsymbol{\theta}; \boldsymbol{\xi}, t_i)}{\partial \theta_j \, \partial \xi_h}\right]_{\substack{\boldsymbol{\theta}=\boldsymbol{\theta}^0 \\ \boldsymbol{\xi}=\boldsymbol{\xi}^0}} \tag{A-20}$$

Also

$$\Delta_u \doteq C + \sum_{h=1}^{k} (\xi_{hu} - \xi_h^0)D_h \tag{A-21}$$

where

$$C = \Delta(\boldsymbol{\psi}, \boldsymbol{\theta}^0; \boldsymbol{\xi}^0, t_i) \tag{A-22}$$

$$D_h = \left[\frac{\partial\{\Delta(\boldsymbol{\psi}, \boldsymbol{\theta}^0; \boldsymbol{\xi}^0, t_i)\}}{\partial \xi_h}\right]_{\boldsymbol{\xi}=\boldsymbol{\xi}^0} \tag{A-23}$$

Hence Equation A-16 can be written as

$$E(\hat{\boldsymbol{\theta}}_u - \boldsymbol{\theta}^0) \doteq \left[\left(A + \sum_{h=1}^{k} (\xi_{hu} - \xi_h^0)B_h\right)'\left(A + \sum_{h=1}^{k} (\xi_{hu} - \xi_h^0)B_h\right)\right]^{-1}$$
$$\cdot\left(A + \sum_{h=1}^{k} (\xi_{hu} - \xi_h^0)B_h\right)'\left(C + \sum_{h=1}^{k} (\xi_{hu} - \xi_h^0)D_h\right) = F(\boldsymbol{\xi}_u - \boldsymbol{\xi}^0) \tag{A-24}$$

Thus we find that when the model is inadequate $E(\hat{\boldsymbol{\theta}}_u - \boldsymbol{\theta}^0)$ will be a function of the levels of ξ.

6. APPENDIX B
SUMMARIZING THE INFORMATION IN THE LIKELIHOOD FUNCTION

It is the likelihood *function* itself (or on the Normal assumption the sum of squares function $S(\boldsymbol{\theta})$) which, when the model is adequate, embodies all the information about the parameter supplied by the data. If the model were *linear* in the parameters then $S(\boldsymbol{\theta})$ would be quadratic in $\boldsymbol{\theta}$ and so could be described entirely in terms of its first and second derivatives with respect to $\boldsymbol{\theta}$. Equivalently, it could be described by the maximising values $\hat{\boldsymbol{\theta}}$ and the second derivatives and if the parameter space were *unrestricted* $\hat{\boldsymbol{\theta}}$ could be located by equating first derivatives to zero. In model analysis, however, the models dealt with are usually *non-linear* in the parameters and the parameter space is often restricted (for example certain parameters are necessarily positive). Special care is therefore needed in analysing $S(\boldsymbol{\theta})$ and in particular graphical analysis can be very informative as we have already indicated. If, however, we are satisfied that $\hat{\boldsymbol{\theta}}$ is not close to a restricting boundary and that the model can be approximated over the ranges of interest by a function linear in $\boldsymbol{\theta}$ (so that $S(\boldsymbol{\theta})$ is approximately locally quadratic over these same ranges) then with N observations and p parameters, we may employ as a measure of precision of the estimates the region R defined by

$$S(\boldsymbol{\theta}) \leq S(\hat{\boldsymbol{\theta}})\left\{1 + \frac{p}{N-p} F_\alpha(p, {}_{iv} - p)\right\} \tag{B-1}$$

where $F_\alpha(p, N - \text{p})$ indicates the α significance level of the F distribution with p and N − p degrees of freedom. This region enclosed by the contour on which S = S($\boldsymbol{\theta}$) provides an approximate $100(1-\alpha)\%$ confidence region. From the Bayesian point of view, R would be a region within which 100 $(1-\alpha)\%$ of the posterior distribution lay, if the prior distribution of $\boldsymbol{\theta}$ could be assumed locally uniform [18,37].

More generally suppose there exist *non-linear* transformations $\varphi_i(\boldsymbol{\theta})$, i = 1, 2, $\cdots$, p, [3A, 27A] of the p parameters $\boldsymbol{\theta}$ in terms of which an adequate representation can be obtained over the region R by the linear expansion

$$\eta_u = f(\boldsymbol{\theta}, \xi) = f_1(\boldsymbol{\phi}, \xi) \doteq f_1(\hat{\boldsymbol{\phi}}, \xi) + \sum_{i=1}^{p} (\phi_i - \hat{\phi}_i)\left[\frac{\partial f_1(\boldsymbol{\phi}, \xi)}{\partial \phi_i}\right]_{\boldsymbol{\phi}=\hat{\boldsymbol{\phi}}} \tag{B-2}$$

In terms of these transformed parameters $\boldsymbol{\phi}$ the region R could alternatively be defined by

$$\frac{1}{2}\sum_{i=1}^{p}\sum_{j=1}^{p} S^{ij}(\phi_i - \hat{\phi}_i)(\phi_j - \hat{\phi}_j) \leq \frac{S(\hat{\boldsymbol{\phi}})p}{N-p} F_\alpha(p, N-p) \tag{B-3}$$

where

$$\frac{1}{2\sigma^2} S^{ij} = \frac{1}{2\sigma^2}\frac{\partial^2 S(\boldsymbol{\phi})}{\partial \phi_i\, \partial \phi_j}\bigg|_{\boldsymbol{\phi}=\hat{\boldsymbol{\phi}}} = -\frac{\partial^2 l(\boldsymbol{\phi})}{\partial \phi_i\, \partial \phi_j}\bigg|_{\boldsymbol{\phi}=\hat{\boldsymbol{\phi}}} \tag{B-4}$$

In the $\boldsymbol{\phi}$ space the region R is thus ellipsoidal.

If the condition B-2 is satisfied ahnost all the important information is contained in the estimates $\hat{\boldsymbol{\phi}}$(or, equivalently, in the corresponding values $\hat{\boldsymbol{\theta}}$) and in the derivatives S^{ij} which as noted in Equation B-4 are proportional to the second derivatives of the log likelihood. These second derivatives, in fact, supply estimates of the variance-covariance matrix of $\hat{\boldsymbol{\phi}}$

$$E(\hat{\phi}_i - \phi_i)(\hat{\phi}_j - \phi_j)' = 2[S^{ij}]^{-1}\sigma^2 \tag{B-5}$$

With condition B-2 satisfied the result applies to small samples but it corresponds to the well-known asymptotic result concerning the variance-covariance matrix and the second derivatives of the log likelihood function. According to this result the asymptotic variance-covariance matrix for $\hat{\boldsymbol{\theta}}$ is given by

$$E(\hat{\theta}_i - \theta_i)(\hat{\theta}_j - \theta_j)' = -\frac{1}{2}\left[\frac{\partial^2 l(\boldsymbol{\theta})}{\partial\theta_i\ \partial\theta_j}\right]^{-1}_{\boldsymbol{\theta}=\hat{\boldsymbol{\theta}}} \tag{B-6}$$

or equivalently with $\hat{\boldsymbol{\phi}}$ by

$$E(\hat{\phi}_i - \phi_i)(\hat{\phi}_j - \phi_j) = -\left[\frac{\partial^2 l(\boldsymbol{\phi})}{\partial\phi_i\ \partial\phi_j}\right]^{-1}_{\boldsymbol{\phi}=\hat{\boldsymbol{\phi}}} = 2[S^{ij}]^{-1}\sigma^2 \tag{B-7}$$

The logic of these results can be seen if we notice that as the number N increases the region over which the condition B-2 needs to apply becomes smaller and smaller, and the non-linear transformations $\phi_i(\boldsymbol{\theta}), i = 1, 2, \ldots, p$, between $\boldsymbol{\theta}$ and $\boldsymbol{\phi}$ will be closely represented by linear transformations which would lead from Equation B-5 to B-6 directly.

To summarize the situation with regard to typifying the likelihood function, in any particular problem one of three circumstances can occur.

(i) It happens quite frequently that an adequate linear approximation of the form of Equation B-2 is available in the original parameterization $\boldsymbol{\theta}$ in which case the above results are approximately justified in terms of the θ's themselves. Virtually all the informationconcerning the estimation situation is then contained in $\hat{\boldsymbol{\theta}}$ and the derivatives

$$\left.\frac{\partial^2 l(\boldsymbol{\theta})}{\partial\phi_i\ \partial\phi_j}\right|_{\boldsymbol{\theta}=\hat{\boldsymbol{\theta}}}$$

(ii) In some cases it may be that the condition B-2 can be satisfied after suitable transformations $\boldsymbol{\phi}(\boldsymbol{\theta})$ have been made on the parameters $\boldsymbol{\theta}$; the summary statistics would then be $\hat{\boldsymbol{\phi}}$ and

$$\left.\frac{\partial^2 l(\boldsymbol{\phi})}{\partial\phi_i\ \partial\phi_j}\right|_{\boldsymbol{\phi}=\hat{\boldsymbol{\phi}}}$$

(iii) In still other cases no transformation of the parameters $\boldsymbol{\theta}$ can satisfy condition B-2 to a sufficient degree of accuracy. It would then be necessary to consider higher order derivatives of the likelihood function to completely exemplify the situation. When condition B-2 cannot be satisfied we say that intrinsic non-linearity exists.

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