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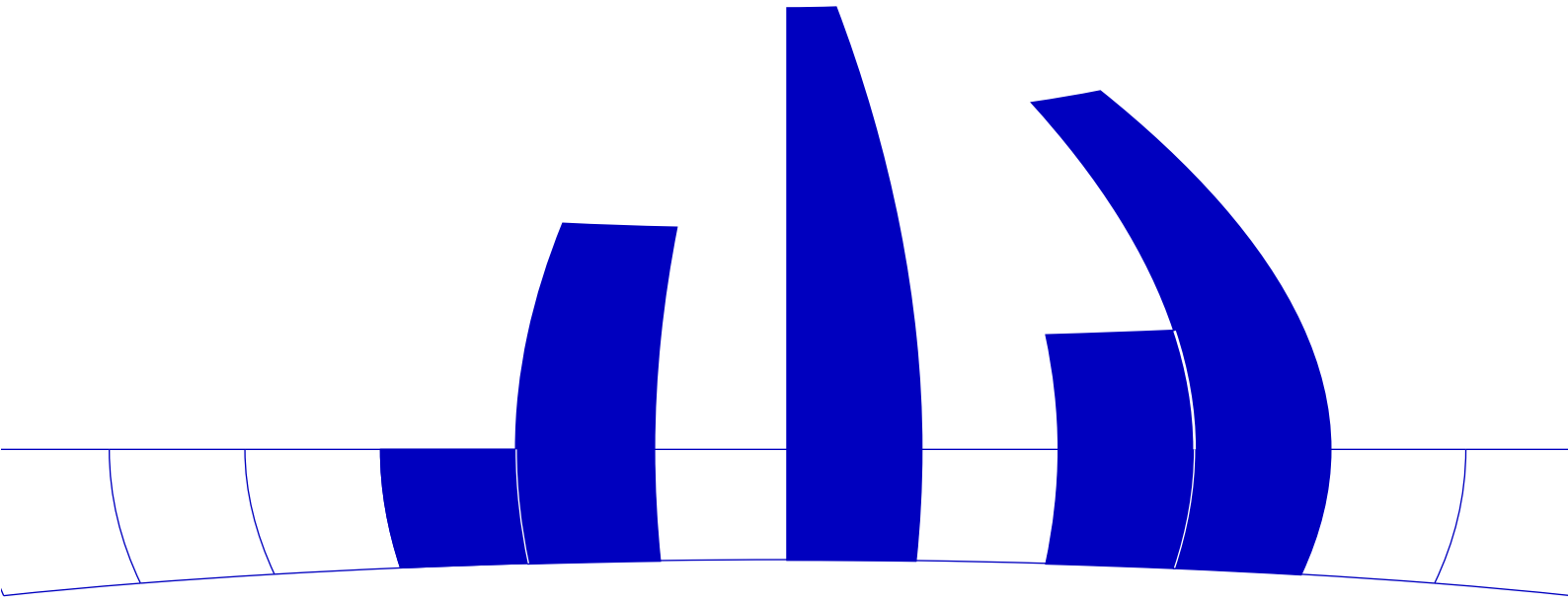

Optimal and Practicable Designs for Measuring Plaque pH-Profiles

by

Valery V. Fedorov[1]
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1 Introduction

The role of plaque acidogenicity in the etiology of caries is probably the main reason for the great interest in measuring plaque pH. Stephan (1940) already observed that if plaque on the tooth surface which is in a neutral status, i.e., has a pH-value close to 7.0, is exposed to carbohydrate the pH rapidly decreases and lateron increases more slowly to approach neutrality; this pattern is called the pH-profile or "Stephan curve". The specific form of the pH-profile determines the caries potential of the particular kind of food; that of an individual determines his/her caries risk.

Traditionally, three methods were developed for measuring plaque pH. The probing method uses a touch electrode and allows the direct reading of the plaque pH from the tooth. The sampling method uses an external electrode system to measure plaque pH in small samples of plaque that are removed from the teeth. Of less practical relevance are indwelling methods that allow continuous measurement by means of an electrode system that is worked into the denture assembly.

Measurement of the pH-profile is of particular interest as its characteristics can be interpreted as indicators of the varying acidogenicity of the substances in our nutrition. Both the probing and the sampling method are routinely applied in measuring

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the pH-profile. A usual approach is to take measurements at regular time intervals over at least 30 minutes after material is taken into the mouth ("uniform design"), or to take measurements at 2, 5, 10, 20, and 30 minutes (Dirksen, 1985).

In this paper we will show that the theory of optimal experimental design leads to quite different patterns of measurement. These patterns take into account (a) the structure of the ongoing process and (b) what parameters or characteristics are object of inference. We will demonstrate that the use of optimal designs or of designs that are close to optimal ones allows to reduce the sample size without decreasing the accuracy of the results.

In Section 2 we present a model that is suitable to describe the pH-profile and we give some justification on an empirical basis. Section 3 discusses optimal experimental designs for estimating the model parameters or other characteristics of the pH-profile. Section 4 gives some numerical illustrations of designs that are optimal or that are derived from the optimal design by taking practicability into account. In the final section, recommendations are given for the practical use of the suggested designs.

2 Model for the Plaque pH-Profile

Typical patterns of the pH-profile are given in *Figure 1.* The figure shows measurements of plaque pH taken by means of the sampling method from twelve individuals in constant time-intervals of four minutes over a period of 28 minutes.[2]

insert Figure 1

A model that can reasonably be interpreted from the theoretical point of view and that is suited to give a good fit to the data has the mean value or response function

$$\mathrm{pH}(t) \;=\; \beta\left[1 + e^{-\theta_1 t} - e^{-\theta_2 t}\right]. \qquad (1)$$

The actual observations deviate from $\mathrm{pH}(t)$ by an additive error term with mean zero and variance σ^2. The parameters of the model can be interpreted as follows:

- β corresponds to the baseline pH, that is the initial value before the treatment is started and the value that is attained asymptotically,
- θ_1 corresponds to the decrease in the first part of the pH-profile, and
- θ_2 corresponds to the increase of the pH-profile.

[2]The authors are grateful to Univ.Prof. Dr. Erich Schuh, Ludwig Boltzmann-Institut für Parodontologie in Baden/Austria, for permitting the use of the data that were measured by members of his Institute.

Conditions for measuring the pH-profile usually include that measurements are taken at least 2.5 hours after the last intake of food or drink. Under this condition the baseline pH is $\beta = 7.0$.

Characteristics of particular interest are the location of the minimum of the pH-profile, the maximal decrease of the profile, i.e., the drop from baseline pH to $\mathrm{pH}(t_{\min})$, and the area bounded by the pH-profile. The minimum is attained at

$$t_{\min} = (\ln \theta_2 - \ln \theta_1)/(\theta_2 - \theta_1)$$

which does not depend on β. The drop $\Delta = \beta - \mathrm{pH}(t_{\min})$ from the baseline pH to the minimum $\mathrm{pH}(t_{\min})$ is a multiple of the initial value β:

$$\Delta = \beta \left[\left(\frac{\theta_1}{\theta_2} \right)^{\frac{\theta_2}{\theta_2 - \theta_1}} - \left(\frac{\theta_1}{\theta_2} \right)^{\frac{\theta_1}{\theta_2 - \theta_1}} \right].$$

The area bounded by the pH-profile is

$$F = \int_0^\infty [\beta - \mathrm{pH}(t)]\, dt = \beta \left(\frac{1}{\theta_1} - \frac{1}{\theta_2} \right).$$

It can be assumed that both the maximal drop Δ and the area F are highly correlated with the caries potential, and both can easily be interpreted in terms of the etiology of caries. Also the time span $t_{\min}$ might be of interest.

The bold line in *Figure 1* is obtained by fitting the curve (1) to the data shown in that figure by means of a nonlinear least squares algorithm; the estimates of the parameters are $\hat{\theta}_1 = 0.67$ and $\hat{\theta}_2 = 0.43$. The figure indicates that the observed pH-values are considerably scattered around the mean curve. This implies the generalization of the nonlinear regression model (1) to a regression model with stochastic parameters. The increase in the explained variation due to the stochastic nature of the parameters is statistically significant.

In the following, we will assume that (1) with $\beta = 7.0$ is the response function of a certain population. For the j-th individual of this population the response function is

$$\mathrm{pH}_j(t) = f(\beta_j, \theta_j, t) = 7.0 \left[1 + e^{-\theta_{1j} t} - e^{-\theta_{2j} t} \right], \qquad (2)$$

where $\theta_j = (\theta_{1j}, \theta_{2j})'$ is a random vector with the population parameters $\mathrm{E}\{\theta_j\} = \theta_0$ and $\mathrm{Var}\{\theta_j\} = \mathcal{D}$.

Typical problems of interest are as follows:

A. The pH-profile related to a specific food-item or characteristics of the profile are to be estimated on the basis of a sample taken from individuals of a certain population. The profile or its characteristics can be used as indicator of the caries-activity of the food-item with respect to that population.

B. The pH-profile related to a standard food-item like sucrose or characteristics of the profile of an individual is to be estimated on the basis of measurements taken from that individual. These characteristics can serve as indicator of the individual's caries-risk.

Among other problems, testing the difference between the pH-profiles related to two food-items might interest. Such a test can be used to proof differences in the caries-activity of the food-item.

In the next section, we will present some results from the theory of experimental design that allow us to optimize in some way our efforts in taking samples. We will concentrate our interest on the two above-mentioned problems A and B. The resulting designs depend not only on the type of estimation problem but also on the characteristic of interest (e.g., θ_j or θ_0, Δ, F, etc.). Estimation procedures for nonlinear regression models with stochastic parameters are discussed by Fedorov *et al.* (1990).

3 Optimal Designs

The main idea of a well-designed experimental plan for parameter estimation is to take a (possibly given) number of measurements in such a way that the precision of the estimates is maximized. In addition, the unbiasedness of the estimates and possible restriction on the experimental conditions (e.g., to a certain experimental region) have to be considered. Similarly, in a hypothesis testing situation, the measurements should be taken such that the power of the test is maximized.

An experiment $\xi(n)$ consists of a set of design points $\{x_1, \ldots, x_n\}$ and a corresponding set of weights $p_i = N_i/N$, $i = 1, \ldots, n$, where N_i is the number of observations taken at x_i and $N = \sum_{i=1}^{n} N_i$ is the total number of observations.

The quality of estimates $\hat{\theta}$ of a k-vector θ of parameters can be expressed by means of bias and covariance matrix of the estimator. In the case of unbiased estimators, an experiment $\xi_1(n)$ with covariance matrix $D_1(\hat{\theta})$ is preferred to an experiment $\xi_2(n)$ with $D_2(\hat{\theta})$, if $D_2(\hat{\theta}) - D_1(\hat{\theta})$ is a positive definite matrix. In general, it is not possible to find a unique optimal design for such an experiment, since the $k \times k$-order of $D(\hat{\theta})$ leads to a multiobjective optimization problem. The common approach to overcome this problem is to use a scalar function $\Phi[D(\hat{\theta})]$ of the covariance matrix D, the so-called design criterion, in order to compromise between different estimates. Frequently used design criteria are

(1) the D-criterion

$$\max_{\xi} |D(\hat{\theta})^{-1}|;$$

it is, due to various advantageous mathematical properties such as scale invariance, the most frequently used criterion; the corresponding estimates are called *D-optimal* estimates.

(2) the trace-criterion

$$\min_{\xi} \operatorname{tr} D(\hat{\theta})\,;$$

here, the sum of variances of the parameter estimates is minimized; the estimates are called *A-optimal* estimates.

Other design criteria aim, e.g., at minimizing the maximal eigenvalue of D (E-optimality) or at minimizing the maximal variance of the estimates.

In applications it might happen that not all components of the parameter vector θ are of same interest. In this situation the design criteria are applied to the approximate covariance matrix

$$f[D(\hat{\theta})] = P^T D(\hat{\theta}) P \tag{3}$$

where the transformation (or so-called interest) matrix P contains corresponding weights. Similarly, if not the parameter vector θ but a function $h(\theta)$ of the parameters is of interest, the design criteria are applied to (3) with

$$P = \left[\frac{\partial}{\partial \theta} h(\theta) \Big|_{\theta=\hat{\theta}} \right] . \tag{4}$$

In the case that only one component is to be estimated, application of both the D- and the trace-criterion as $P^T D(\hat{\theta}) P$ means minimizing the variance of the estimate.

The optimal design theory deals with solving the minimization problem related to the design criterion that is to be applied. The main results are so-called equivalence theorems that state relations between different optimality criteria. Surveys on optimal design theory and equivalence theorems give Fedorov (1972) and Silvey (1980). Härtler (1976) discusses the subject with emphasis on application in fields such as biometry.

The numerical algorithms that are most commonly used in applying the design criteria are an iterative procedure of first order and an exchange-type algorithm. For applications the exchange-type algorithm is preferable since it implicitely obeyes the restriction of one possible observation per design point or time-unit. Numerical algorithms are surveyed by Silvey (1980); details of exchange-type algorithm can be found in the paper by Fedorov (1989).

4 Practicable Designs

As stated in Section 2, the pH-profile of an individual can be modelled as a realization of nonlinear regression on time with stochastic parameters. We aim at estimating model parameters and characteristics of the pH-profile like the maximal drop Δ or the area F for a particular population or for an individual.

Designs that are to be applied in practical research have to fulfill requirements of practicability that are imposed by the needs and possibilities of the experimental

situation. Examples of such requirements are that a minimal amount of time has to pass between two measurements, or that the overall duration of the test procedure has to be limited. In the following we first will derive optimal designs and see lateron how these designs are affected if restrictions due to practicability are imposed. The minimal time span between two measurements is set to two minutes.

4.1 Individual profiles

In the following we will assume in certain cases that the true values of the population parameters θ_0, $\mathcal{D}$, and σ^2 are known to be

$$\hat{\theta}_0 = \begin{bmatrix} 0.67 \\ 0.43 \end{bmatrix}, \quad \hat{\mathcal{D}} = \begin{bmatrix} 0.00723 & 0.01072 \\ 0.01072 & 0.01636 \end{bmatrix}, \quad s^2 = 0.047,$$

the estimates obtained from the data shown in *Figure 1*. In such cases we say that the design makes use of *prior* information.

Figure 2 shows the D-optimal design for the parameters θ_j that does not make use of *prior* information. In agreement with the optimal design theory, it consists of two measurements. One measurement has to be taken in the decreasing and one in the increasing part of the pH-profile. If we want to take eight measurements, the corresponding (restricted) D-optimal design spreads them as close as possible around the optimal measurements as shown in *Figure 3*. The analogous D-optimal design that in addition makes use of *prior* information is shown in *Figure 4*. All measurements have to be taken around the minimum of the pH-profile. The D-optimal designs for both Δ and F of an individual's pH-profile that make use of *prior* information coincide with the design shown in *Figure 4*.

insert Figure 2

insert Figure 3

insert Figure 4

The result that the optimal estimate for Δ (or F) is obtained if we position all observations close to the point where the pH-profile has its minimum, i.e., where this maximal drop of the pH is reached is certainly very plausible. This result is very robust to changes in the parameters θ_0, $\mathcal{D}$, and σ^2 as well as to changes in the minimal time span between two measurements that was set to two minutes in our study.

The designs will certainly change if we assume that the baseline pH-value β is unknown. However, in most investigations this assumption is acceptable as we can ask our patients to comply with the corresponding condition.

4.2 Estimation of population parameters

The assumption that the population parameters θ_0, $\mathcal{D}$, and σ^2 are known cannot be justified if we are concerned with a new substance or a population for which this knowledge is not available. Optimal designs for estimating these parameters are comprehensively discussed by Fedorov et al. (1990). In many cases the most crucial parameter is θ_0. However, the effort in getting the estimate $\hat{\theta}_0$ is a unique one; therefore, the possible reduction in effort due to an improved design is not essential. On the other hand, a non-optimal design is more robust than the optimal one with respect to assumptions that are needed in the construction of the design.

5 Comparison of Designs for Measuring Plaque pH-Profiles

Comparison of the performance of various designs for estimating a parameter or characteristic can be based on the dual function which in the case of D-optimality is the variance of the response function. The dual function depends on the design point and is shown for the above-mentioned optimal designs in the respective figures.

To assess the relative merits of the optimal design given in *Figure 4* we compare it with the traditional standard design, i.e., the uniform design that extends over 28 minutes. *Figure 5* shows the maximal variance of the response function for estimating the maximal drop Δ for the uniform and for the optimal design for sample sizes two to eight. It can be read from this figure that e.g. the maximal variance of the estimate for Δ when using the optimal design based on five observations is less than the one with eight observations in the uniform of design. This indicates clear economic advantages of the optimal design.

insert Figure 5

Beyond the economic aspects, advantages in terms of inconvenience for the patients can be seen: The amount of time needed for the optimal design (14 minutes) is one half of what is necessary for the uniform design (28 minutes). Of course, the readiness of patients to comply with the procedure can easier be attained if conditions are less demanding.

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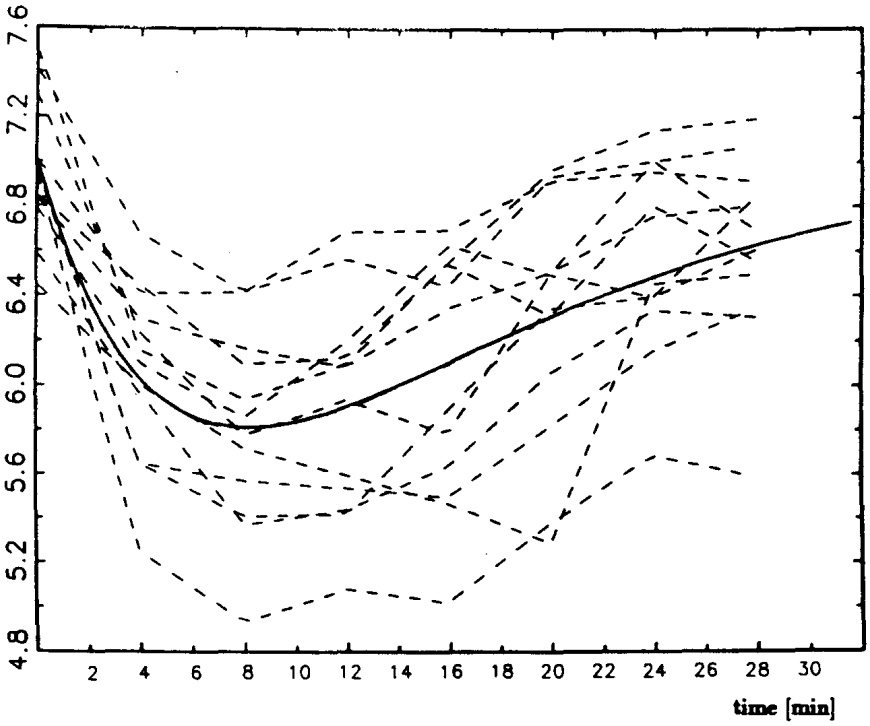

Figure 1: Measurements of the Stephan curve, taken by probing after rinsing with sucrose, and fitted curve.

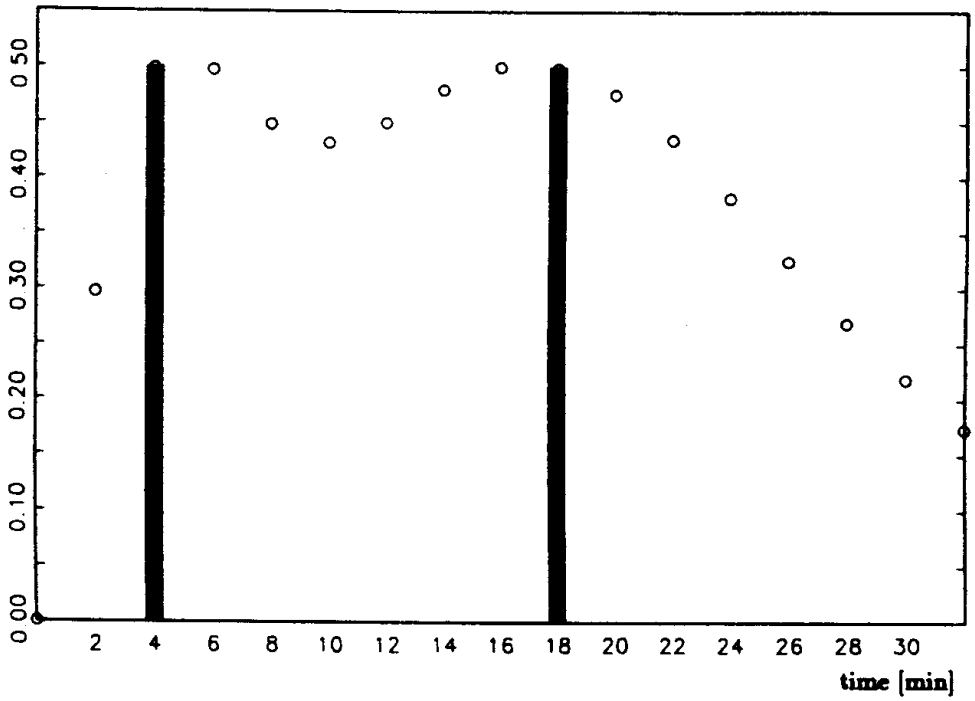

Figure 2: D-optimal design and dual function for estimating individual parameters θ_j; no use of *prior* information.

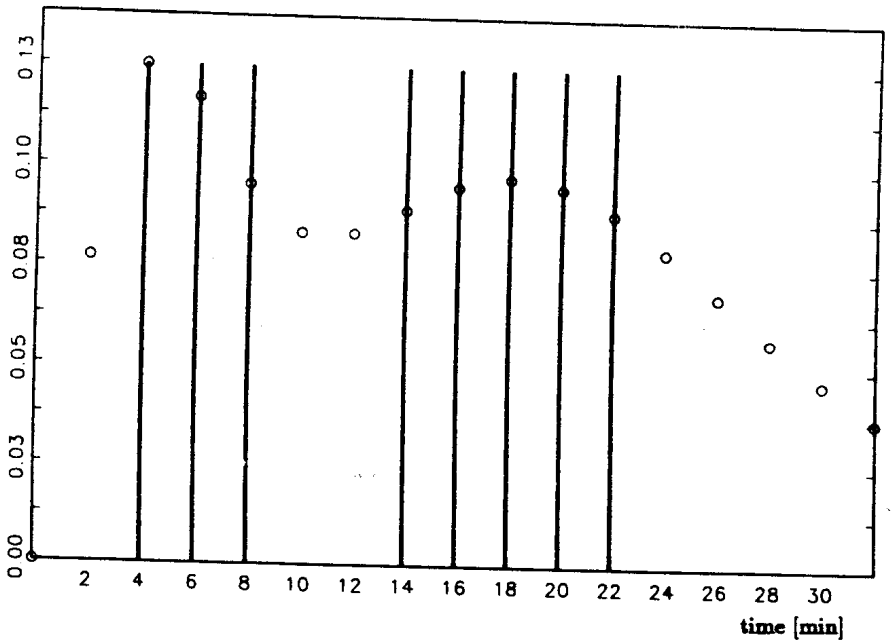

Figure 3: D-optimal design for eight observations and dual function for estimating individual parameters θ_j; no use of ***prior*** information.

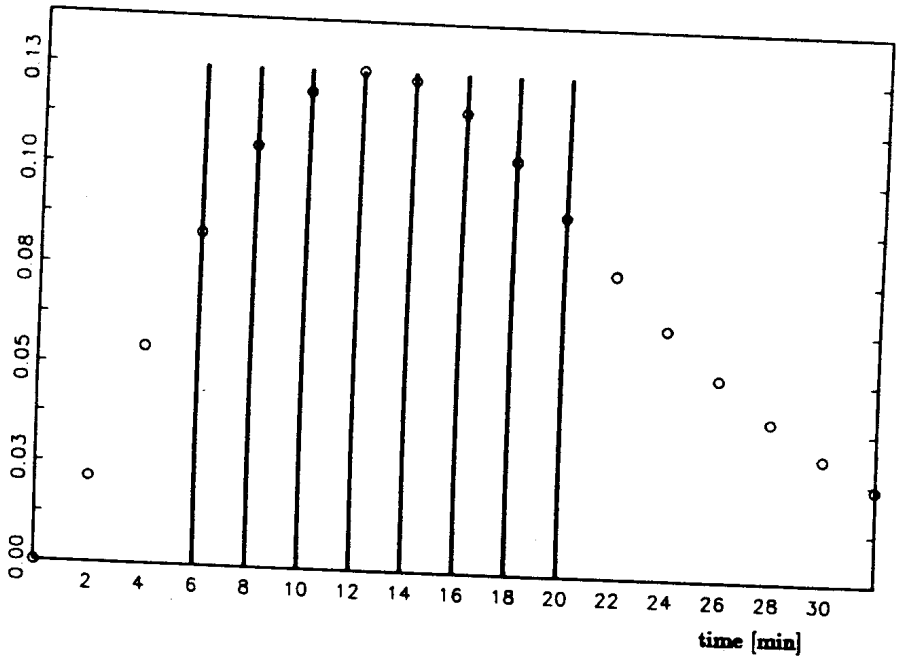

Figure 4: D-optimal design for eight observations and dual function for estimating individual parameters θ_j that makes use of *prior* information.

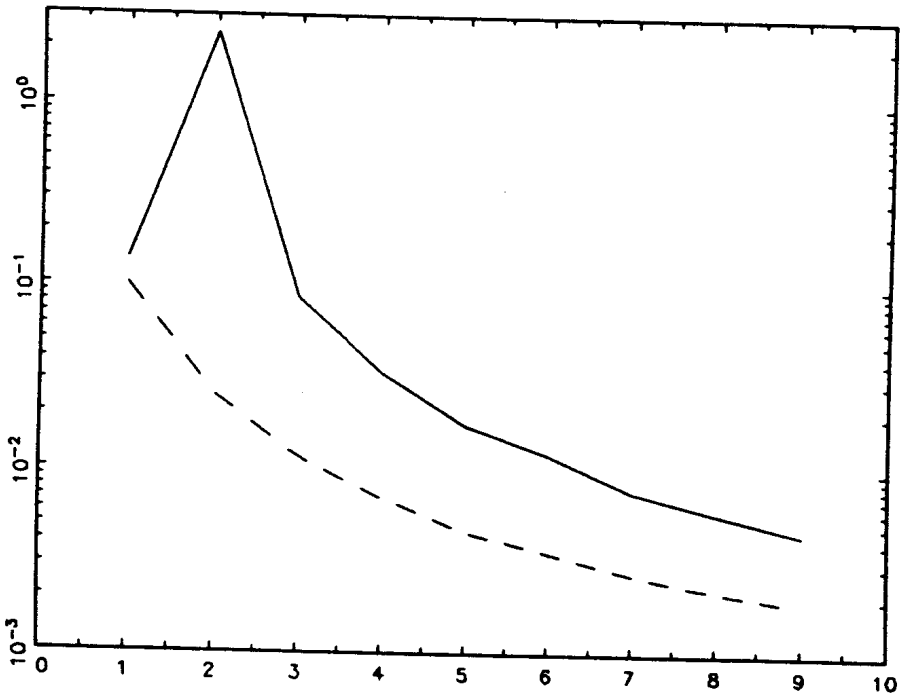

Figure 5: Maximal variance of the response function for (a) the uniform (solid line) and (b) the D-optimal design with use of *prior* information (dashed line) for estimating the maximal drop Δ, as a function of the sample size.