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COMPARISON OF BIAS-REDUCING METHODS FOR ESTIMATING THE PARAMETER IN DILUTION SERIES

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ABSTRACT

Ten different estimators of the parameter in a limiting or serial dilution assay are compared. Eight of them are constructed to reduce the bias of the commonly used maximum likelihood estimator. Extensive Monte Carlo experiments using various designs, suggest that a particular jackknife version of the maximum likelihood estimator is preferred, provided that the design is not too small.

1. INTRODUCTION

Limiting and Serial Dilution Assays (LDA and SDA) are widely used in many areas, including public hygiene, bacteriology, biology and immunology; see Taswell (1987). In general these assays are primarily intended to estimate the relative frequency of a well-defined cell in a population of cells or the average number of organisms per unit volume of solution. In both LDA and SDA this parameter is commonly estimated by using the "single-hit Poisson model" with quantal data yielded by samples taken from different dilutions. The assumptions underlying this model are well-known (see Finney (1978), Taswell (1981)) and will be described briefly, using the terminolology of LDA. A test preparation contains numerous cells of which an unknown proportion φ has a certain property, for example immuno-competency. From this test preparation, m different dilutions are prepared. Then, from dilution j, n_j replicate cultures are taken. The number of cells in the k-th replicate culture of dilution j is a Poisson distributed variable with mean x_j. A fraction φ of these cells has the intended property. A further assumption is that a positive response is obtained for a replicate culture, if and only if at least one cell of the specific type is present.

Statisticians can contribute to the execution of a LDA or a SDA in at least two ways. They can help the experimenter to construct an experimental design which will take advantage of existing a priori information. This hopefully precludes experimentation yielding useless data, and it enables adjusting the precision of an estimator. Furthermore they can advise on the statistical techniques to be used. In many applications of dilution analysis, the assays are very expensive and time consuming, while in some circumstances they are not repeatable either. In these cases it is of vital interest to carefully chose an experimental design and a statistical estimator minimizing bias and standard error. Recent research has been done on design problems (Loyer (1981), Taswell (1987) and Strijbosch et al. (1987)), and Monte Carlo studies have been made on the choice of the statistical procedure to be used (Salama et al. (1978), Loyer (1981), Taswell (1981), Strijbosch et al. (1987) and Does et al. (1988)). The results of these Monte Carlo studies cannot be compared properly because of the absence of generally accepted design methods: most authors used different experimental designs, when generating the simulation results. It is obvious that the statistical properties of the possible estimators are dependent on the design used. If these properties do not hold over other possible designs it could easily occur, that one author finds that estimator 1 is better than estimator 2 while another author finds conflicting results.

This paper is organized as follows. Section 2 describes the experimental design, which has been used to compare different estimators. Section 3 discusses ten different estimators for the parameter in dilution series. The last two Sections are devoted to the Monte Carlo experiments and the results, respectively.

2. EXPERIMENTAL DESIGN

It is a very important issue, when comparing statistical estimators, to use a design which can be considered as a reference and a frame. The design method proposed by Strijbosch et al. (1987) seems to be a good candidate for use in general dilution assays and in Monte Carlo comparisons. First some notation will be introduced. Let the number of groups of replicate cultures be denoted by m, the (mean) number of cells tested in a replicate culture of group j by x_j, and the number of replicate cultures for group j by n_j, $j=1,\dots,m$. Furthermore let φ denote the unknown frequency.

It is convenient to split the total design problem into two parts. Firstly, the design parameters m, and $x_1,\dots,x_m$ are determined; secondly, the numbers of replicate cultures $n_1,\dots,n_m$ are chosen such that the expected bias and the expected standard error of an estimator are within certain bounds. The efficacy of Strijbosch et al. (1987)'s method for determining the design parameters m and $x_1,\dots,x_m$ can be explained as follows. A researcher setting up a dilution assay, will in general have some prior information about the value of φ. It is natural to think of a lower bound φ_1 and an upper bound φ_2 for φ. He wants to plan his assay such that not too many fractions of negatively responding cultures are too close to either zero or one. There must be enough dilutions which yield fractions of negatively responding cultures, somewhere in the middle between zero and one. This must be true for every value of φ which could be the true value according to the prior information of the experimenter, that is, for every φ satisfying $\varphi_1 \leq \varphi \leq \varphi_2$. We must be more specific in order to deduct design formulae from these general set-up considerations. If only fractions between certain values P_1 and P_2 are called sufficiently informative and if we want to have (on the average) d fractions between these values for each possible φ in the range $[\varphi_1,\varphi_2]$, then the design parameters m and $x_1,\ldots,x_m$ can be chosen according the formulae (i) through (iv) in Strijbosch et al. (1987). The advantages of this design method are: it incorporates researcher's criteria, it has suitable properties, and it can be easily used in Monte Carlo experiments aimed at a meaningful comparison of statistical estimators.

The most interesting statistical estimators for which comparisons are made in the various studies mentioned before, will be compared in this study, namely the minimum chi-square method (MC), the maximum likelihood method (ML) (see Taswell (1981)), three jackknife versions (Jr,Jc, and Je) of the ML estimator (see Does et al. (1988)), two methods (S1 and S2) invented by Salama et al. (1978), and three bootstrap versions (Br,Bc, and Be) of the ML estimator. In the next Section these estimators will be described briefly.

3. STATISTICAL METHODS

3.1 Notation

In Section 2 we introduced the following notation: m equals the number of groups of replicate cultures, x_j equals the (mean) number of cells tested in a replicate culture of group j, n_j equals the number of replicate cultures for group j, j=1,...,m, and φ denotes the unknown frequency. Then the data of the biometrical model can be represented as follows :

$$\{Y_{jk}\}\ j=1,\ldots,m;\ k=1,\ldots,n_j, \tag{1}$$

where Y_{jk} are independent Bernoulli distributed variables, with $P(Y_{jk}=0) = 1 - P(Y_{jk}=1) = \exp(-\varphi x_j)$. A negative respons for a replicate culture is thus denoted by zero.

3.2 The Maximum Likelihood Method

From (1) it follows that the logarithm of the likelihood function $L(\varphi)$ is given by

$$\log L(\varphi) = \Sigma_{j=1}^{m} \Sigma_{k=1}^{n_j} \{-(1-Y_{jk})\varphi x_j + Y_{jk}\log(1-\exp(-\varphi x_j))\}. \tag{2}$$

The ML estimator ($\hat{\varphi}_{ML}$) is the value of φ that maximizes (2). As is pointed out in Does et al. (1988), this estimator must be slightly adapted in order to obtain an estimator with finite bias. If all Y_{jk} equal 1 (this event occurs with a small but positive probability), then the ML estimate equals infinity and hence $E(\hat{\varphi}_{ML})=\infty$, thus leading to an infinite, rather than an asymptotically negligible bias. Does et al. (1988) proposed the following modification: whenever $Y_{jk}=1$ for $j=1,\ldots,m$, $k=1,\ldots,n_j$ replace one Y_{jk}, for example the most suitable such as Y_{11}, by 0. It is shown that this simple modification suffices to reduce the bias from infinity to the desired order. This adaptation of $\hat{\varphi}_{ML}$ will be assumed throughout the paper.

Sufficiency implies that the relevant observations from a LDA consist of the independent binomial random variables R_j defined by $R_j = \Sigma_{k=1}^{n_j} (1-Y_{jk})$. The vector $(R_1,\ldots,R_m)$ will be denoted by $\underline{R}$. Furthermore let n_j-R_j be denoted by Q_j and $(Q_1,\ldots,Q_m)$ by $\underline{Q}$.

3.3 Three Jackknife Versions of the ML Estimator

In general the jackknife is defined as follows. Suppose a parameter Θ is estimated on the basis of the stochastic variables

$X_1,\dots,X_N$. Consider an estimate $T_N=T_N(X_1,\dots,X_N)$. Then the i-th jackknifed pseudo-value is defined as

$$T^J_{Ni} = NT_N-(N-1)T_{N-1}(X_1,\dots,X_{i-1},X_{i+1},\dots,X_N),\ i=1,\dots,N. \qquad (3)$$

The jackknife estimator T^J_N defined by

$$T^J_N = N^{-1}\ \Sigma^N_{i=1}\ T^J_{Ni} \qquad (4)$$

reduces the bias in many cases (see Efron (1982)). In our case, the pseudo-values in (3) can be obtained in three different ways. When n_j=n the biometrical model (1) is a matrix with columns that are independent, identically distributed (iid) random vectors. As jackknife estimates are in general determined from iid variables, the natural way to jackknife is to drop one column from (1) at a time (see Strijbosch et al. (1987), and Kleijnen et al. (1987)); this yields the jackknife estimate $\hat{\varphi}_{Jc}$. The two other versions are non-iid cases and are obtained by deleting one row at a time (yielding $\hat{\varphi}_{Jr}$) or one element at a time (yielding $\hat{\varphi}_{Je}$), respectively (see Does et al. (1988)). Note that these last two estimates can be obtained from $\underline{R}$.

3.4 Three Bootstrap Versions of the ML Estimator

Analogous to the three jackknife versions there are three bootstrap versions $\hat{\varphi}_{Bc}$, $\hat{\varphi}_{Br}$, and $\hat{\varphi}_{Be}$. Suppose again that $T_N = T_N(X_1,\dots,X_N)$ is an estimate of the parameter Θ. The ordinary bootstrap approach consists of drawing M random samples $(X^i_1,\dots,X^i_N)_{i=1,\dots,M}$ of size N from $X_1,\dots,X_N$ (see Efron (1982)). Such a sample is obtained by computer generated random sampling with replacement. Although there exist more elaborated bootstrap methods (see Davison et al. (1986)) the simple bootstrap will be used. The i-th bootstrapped pseudo-value is defined as

$$T^B_{Ni} = T_N(X^i_1,\dots,X^i_N),\ i=1,\dots,M. \qquad (5)$$

The bootstrap estimator T^B_N defined by

$$T_N^B = M^{-1} \Sigma_{i=1}^{M} T_{Ni}^B \tag{6}$$

could potentially reduce the bias when estimating the parameter in LDA. As discussed in the previous subsection (§3.3), there are three different ways to define a set $(X_1,\ldots,X_N)$ from the biometrical model (1), thus resulting in the bootstrap estimators $\hat{\varphi}_{Bc}$, $\hat{\varphi}_{Br}$ and $\hat{\varphi}_{Be}$. As before the c-variant represents the iid-case, and is only applicable when all $n_j=n$, $j=1,\ldots,m$.

3.5 Salama et al. (1978) Bias-Reducing Methods

Using Taylor expansions and implicit function theorems, Salama et al. (1978) showed the existence of functions $H(\underline{Q},\hat{\varphi}_{ML})$ such that the estimator $\hat{\varphi}_S$ defined by

$$\hat{\varphi}_S = \hat{\varphi}_{ML} - H(\underline{Q},\hat{\varphi}_{ML}) \tag{7}$$

satisfies

$$E(\hat{\varphi}_S) = \varphi + \Sigma_{j=1}^{m} \mathcal{O}(n_j^{-2}), \tag{8}$$

thus removing the first order bias term. The following two alternatives for the function H are given (yielding the estimators $\hat{\varphi}_{S1}$ and $\hat{\varphi}_{S2}$):

$$G_1(\underline{Q},\hat{\varphi}_{ML}) = \frac{1}{2} \Sigma_{j=1}^{m} \left(\frac{\partial^2 \hat{\varphi}_{ML}}{\partial Q_j^2}\right) n_j \, e^{-\hat{\varphi}_{ML} x_j} (1-e^{-\hat{\varphi}_{ML} x_j}) \tag{9}$$

and

$$G_2(\underline{Q},\hat{\varphi}_{ML}) = \frac{1}{2} \Sigma_{j=1}^{m} \left(\frac{\partial^2 \hat{\varphi}_{ML}}{\partial Q_j^2}\right)_{\underline{u}} n_j \, e^{-\hat{\varphi}_{ML} x_j} (1-e^{-\hat{\varphi}_{ML} x_j}). \tag{10}$$

The second order derivatives in the right-hand side of (10) are evaluated at $\underline{u}$, defined by $\underline{u} = E(\underline{Q})$. Unfortunately the formula given by Salama et al. (1978) for $\frac{\partial^2 \hat{\varphi}_{ML}}{\partial Q_j^2}$ shows typing errors. The correct formula is :

$$\frac{\partial^2 \hat{\varphi}_{ML}}{\partial Q_j^2} = \frac{F_j^2}{D^3} \left\{ \Sigma_{i=1}^{m} Q_i e^{-\hat{\varphi}_{ML} x_i} F_i^2 (x_i + 2F_i e^{-\hat{\varphi}_{ML} x_i}) \right\}$$

$$- 2 \frac{F_j^3}{D^2} e^{-\hat{\varphi}_{ML} x_j}, \qquad (11)$$

where F_i and D are defined by, respectively,

$$F_i = F_i(\hat{\varphi}_{ML}) = x_i / (1-e^{-\hat{\varphi}_{ML} x_i}) \qquad (12)$$

and

$$D = D(\underline{Q}, \hat{\varphi}_{ML}) = \Sigma_{j=1}^{m} Q_j e^{-\hat{\varphi}_{ML} x_j} F_j^2. \qquad (13)$$

Salama et al. (1978) used a special modification of the ML estimator, in case all Q_j equal n_j, j=1,...,m. That modification is essentially the same as described earlier in the subsection of the ML method (§3.2).

3.6 The Minimum Chi-Square Method

The Minimum Chi-Square or MC estimator ($\hat{\varphi}_{MC}$) is determined as the value of φ that minimizes

$$\chi^2(\varphi) = \Sigma_{j=1}^{m} \frac{(R_j - n_j \exp(-\varphi x_j))^2}{(n_j \exp(-\varphi x_j)(1-\exp(-\varphi x_j))} . \qquad (14)$$

Since the expected value of the MC estimator is infinite, $\hat{\varphi}_{MC}$ has been adapted in the same manner as $\hat{\varphi}_{ML}$ has; see §3.2.

4. MONTE CARLO EXPERIMENTS

An extended version of the simulation program described in Does et al. (1988) has been used for our Monte Carlo experiments. The modification consisted of the addition of the three bootstrap estimators, the two methods of Salama et al. (1978), and the MC estimator. Much care has been taken to test the program. For example, the results of Salama et al. (1978) which have been based on the exact distributions of $\hat{\varphi}_{S1}$ and $\hat{\varphi}_{S2}$ could be reproduced quite satisfactorily in the simulations. In this paper the statistical estimators are compared for two different designs with three and two different values, respectively, for the number of replicates (n). Thus, using the design method described in Section 2, the following values of $\varphi_1, \varphi_2, P_1, P_2$ and d have been chosen : $\varphi_1=0.001$, $\varphi_2=0.01$, $P_1=0.15$, $P_2=0.70$, d=2 (yielding m=4) and d=3 (yielding m=7). For the case d=2 the simulation program has been executed with n=6, 12 and 18 and in the case d=3, with n=6 and 12. Simulation results have been obtained for 19 equidistant values of φ within the interval $[\varphi_1, \varphi_2]$. The number of generated samples for each combination of $\varphi_1, \varphi_2, P_1, P_2$, d, n and φ was 1,000. The number of bootstrap samples (M) was 100.

The simulation program has been written in PASCAL and uses the NAG (Fortran) subroutines G05DZF and G05DYF for the generation of the Bernoulli variables $\{Y_{jk}\}$ and the bootstrap samples, respectively. The structure of the program will be described briefly for the case d=2. For each of the 19 values of φ, a matrix $\{y_{jk}\}$, j=1,...,4; k=1,...,18 is generated 1,000 times. These numbers are used twice : one time for n=18 and one time for either n=6 or n=12. This concession has been made in order to curtail the required CPU-time. Depending on the value of n, the numbers r_j are determined by $r_j = n - \sum_k y_{jk}$, where k=1,...,6 for n=6, k=7,...,18 for n=12 and k=1,...,18 for n=18. Thus 1,000 datasets (x_j, r_j, n), j=1,...,4 result for each combination of φ and n. For each dataset the program calculates, if possible, the weighted-mean estimate φ_0 (see Taswell (1981)). When all r_j=0 or n, this estimate cannot be determined. In that case $\varphi_0=(\varphi_1+\varphi_2)/2$ has been taken. φ_0 served as an initial estimate for the iterative determination of $\hat{\varphi}_{ML}$. $\hat{\varphi}_{ML}$ served as an initial estimate for the determination of $\hat{\varphi}_{MC}$, the jackknife, and the bootstrap pseudo-estimates. Comparison of the statistical estimators has been based on the mean relative bias (MRB) and the coefficient of variation (CV), defined as follows :

$$\mathrm{MRB} = \varphi^{-1} \Sigma_{t=1}^{1,000} (\hat{\varphi}_t - \varphi)/1,000 \tag{15}$$

and

$$\mathrm{CV} = \varphi^{-1}\left\{ \Sigma_{t=1}^{1,000} (\hat{\varphi}_t - \varphi)^2/1,000 \right\}^{1/2}. \tag{16}$$

The simulations used 59 hours of CPU-time on a VAX 8700 computer.

5. RESULTS AND CONCLUSIONS

The uncorrected ML estimator exhibits a positive bias. Theoretically this is due to the fact that there is a positive probability that all dilutions will produce growth so that the ML estimate becomes infinite. In practice, when m and $n_j, j=1,\ldots,m$ are large enough, this situation will not occur, and Monte Carlo simulations reveal the positive bias in that case. Resampling plans such as the jackknife and the bootstrap are designed to reduce the bias (see Section 3). The Monte Carlo results in Strijbosch et al. (1987) showed that jackknifing in LDA reduces both the bias and the mean squared error of the estimator. Does et al. (1988) explained that there are three different ways of constructing a jackknife estimator in dilution analysis. It is made plausible that all three jackknife estimators reduce the bias by eliminating the first order bias term, and Monte Carlo simulations showed the relative properties of these estimators with respect to the ML estimator for various designs. The three bootstrap versions of the ML estimator can be obtained in a similar way. The two bias-reducing methods in Salama et al. (1978) eliminate the first-order bias term in a way different from jackknifing and bootstrapping, and therefore it is interesting to compare these estimators. From former results (see Strijbosch et al. (1987) and Fazekas de St. Groth (1982)) it is clear that the MC estimator is not attractive. Nevertheless this method is also considered in the Monte Carlo comparisons, especially because of the curious and inconsistent behaviour of its bias and mean squared error.

In the Figures 1a through 5b not all methods are included, in order to prevent confusion resulting from too many curves. For each category only the "best" one is shown. Does et al. (1988) concluded that, among the three jackknife estimators, $\hat{\varphi}_{Je}$ is the best. The present results confirm this conclusion. Thus $\hat{\varphi}_{Jr}$ and $\hat{\varphi}_{Jc}$ are not shown in the Figures. Comparing the simulation results for the three bootstrap estimates, $\hat{\varphi}_{Br}$ is obviously the best estimator. In general, the results tend to be such, that $MRB(\hat{\varphi}_{Be}) \sim 2*MRB(\hat{\varphi}_{ML})$ and $MRB(\hat{\varphi}_{Br}) < MRB(\hat{\varphi}_{Bc}) \leq MRB(\hat{\varphi}_{Be})$. The coefficients of variation for the three bootstrap estimators are more comparable. Thus $\hat{\varphi}_{Bc}$ and $\hat{\varphi}_{Be}$ are not presented in the Figures. The estimates of Salama et al. (1978) have nearly equal MRB and CV. However, there might be a slight preference for $\hat{\varphi}_{S2}$. Thus $\hat{\varphi}_{S1}$ is not included in the Figures. When comparing the remaining five estimators in the Figures 1a through 5b, it becomes clear that in general the estimators $\hat{\varphi}_{Je}$ and $\hat{\varphi}_{S2}$ should be preferred. In small designs, however, the jackknife estimator has the undesired property of a strongly increasing CV for values of φ near φ_2 which can be explained by the frequent occurrence of the situation that all Y_{jk} equal 1 when calculating the pseudo-estimates (see Figure 1b). An attractive property of the jackknife is that it also yields the variance estimate used to determine proper confidence bounds for φ. A major disadvantage of the estimating methods of Salama et al. (1978) is the lack of an estimator for the variance.

Provided that an experimenter works with designs, which are not too small (the design of Figure 4 seems to be large enough), it is clear that the jackknife version of the ML estimator - obtained by leaving out one element at a time - is the statistical procedure of choice.

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Figure 1a

$\varphi 1=.001\ \varphi 2=.01\ p1=.15\ p2=.70\ d=2\ m=4\ n=6$

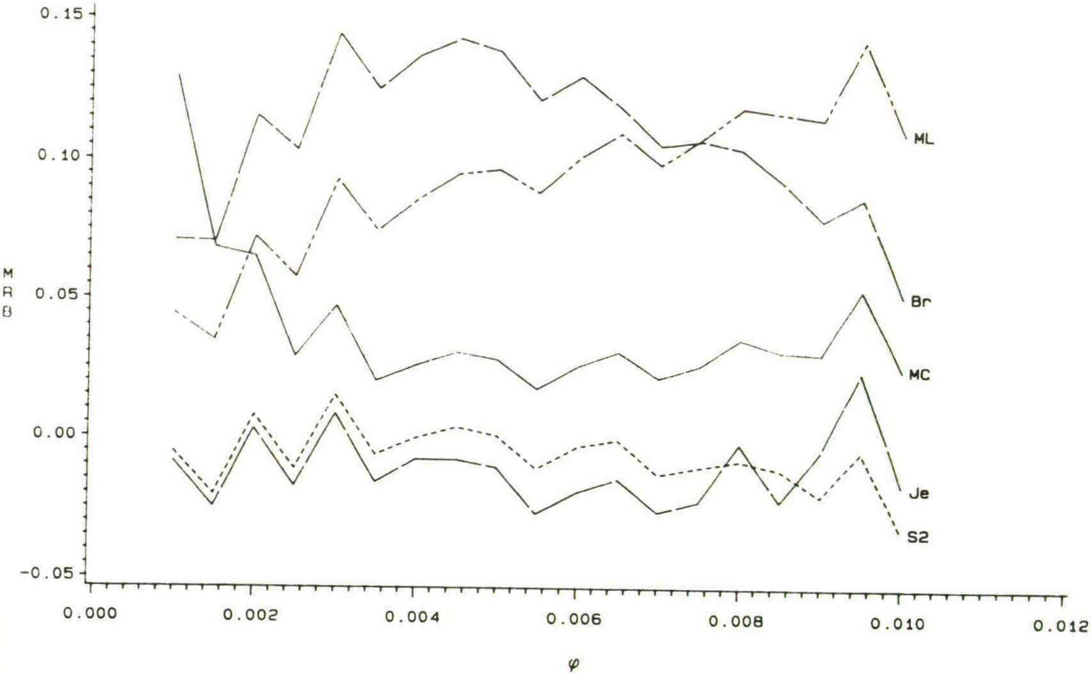


Figure 1b

$\varphi 1=.001\ \varphi 2=.01\ p1=.15\ p2=.70\ d=2\ m=4\ n=6$

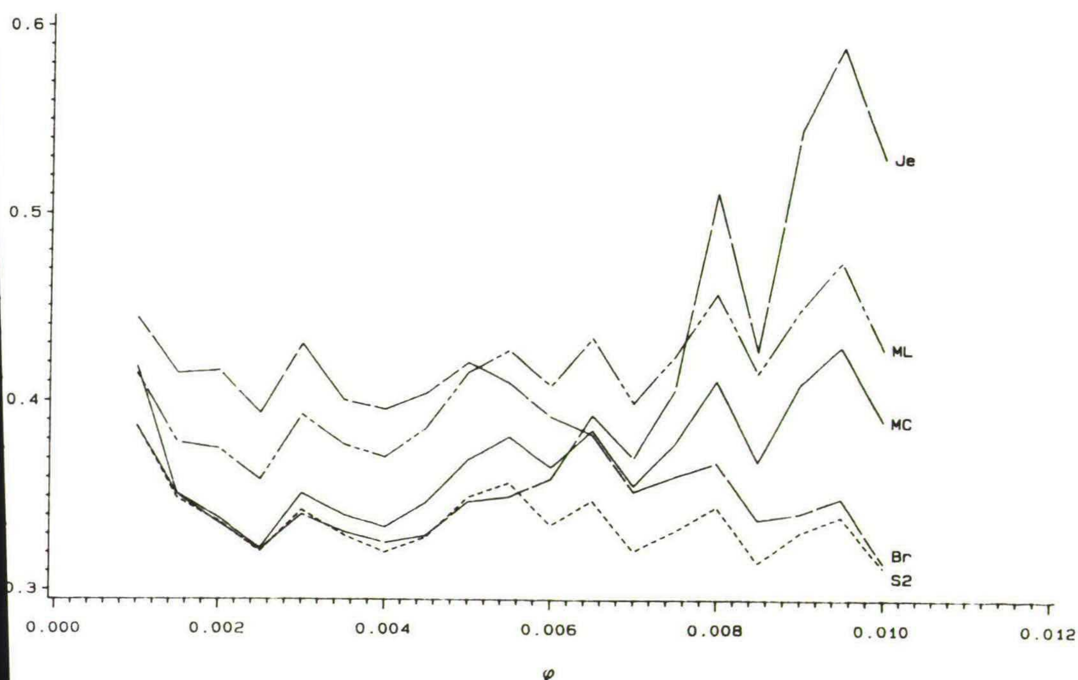


Figure 2a

$\varphi 1 = .001$ $\varphi 2 = .01$ p1=.15 p2=.70 d=2 m=4 n=12

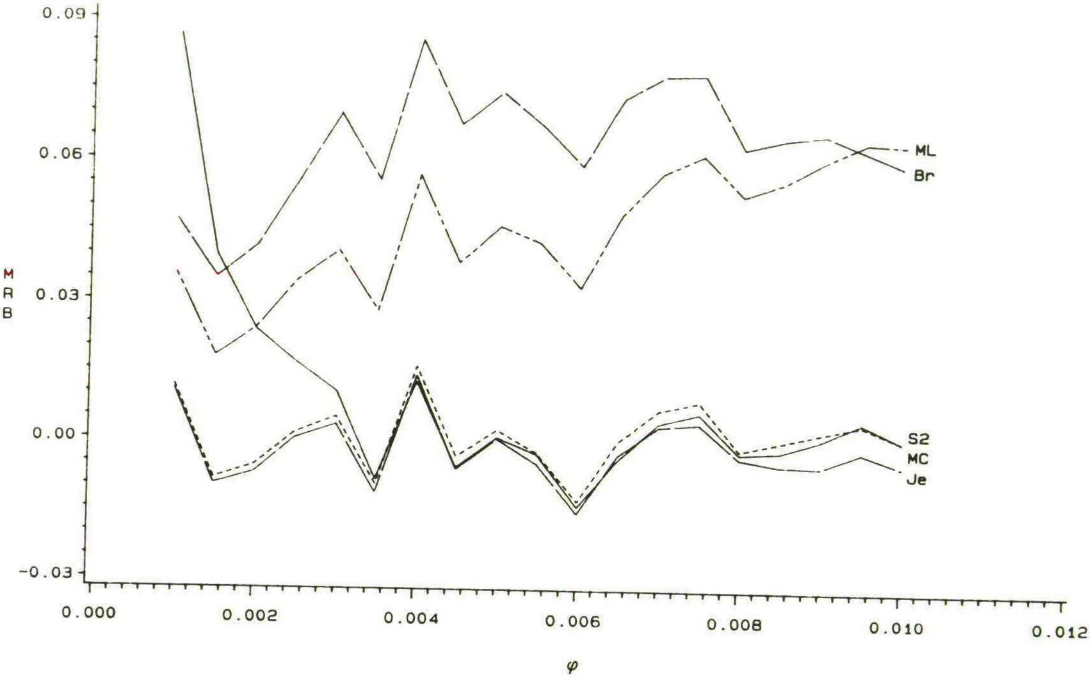


Figure 2b

$\varphi 1 = .001$ $\varphi 2 = .01$ p1=.15 p2=.70 d=2 m=4 n=12

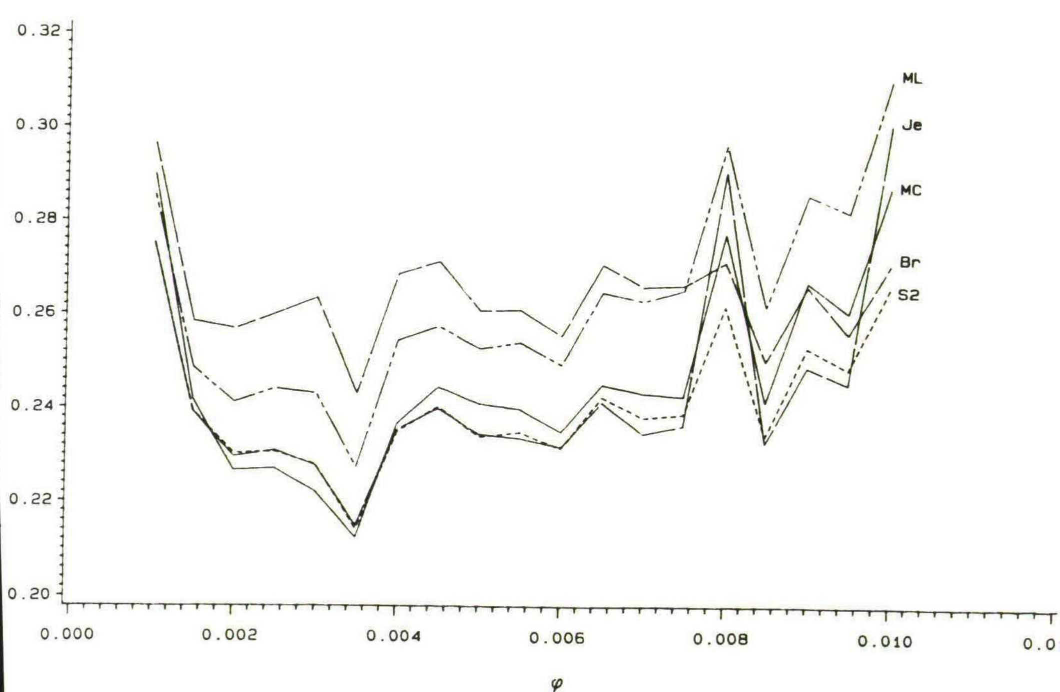


Figure 3a

$\varphi 1=.001$ $\varphi 2=.01$ p1=.15 p2=.70 d=2 m=4 n=18

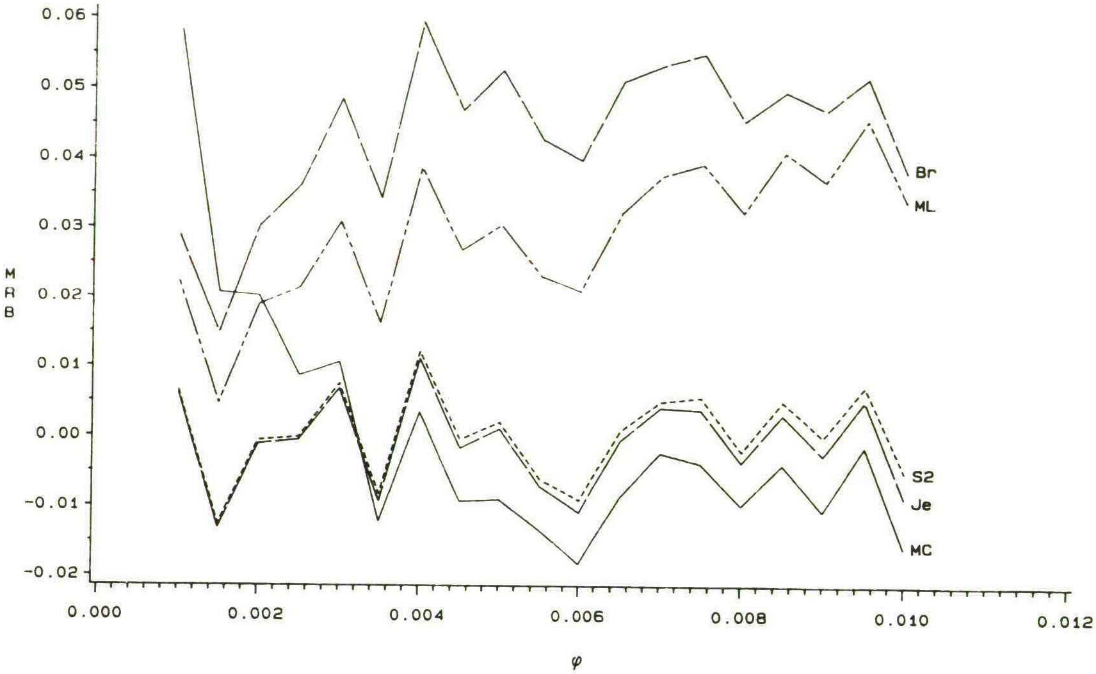


Figure 3b

$\varphi 1=.001$ $\varphi 2=.01$ p1=.15 p2=.70 d=2 m=4 n=18

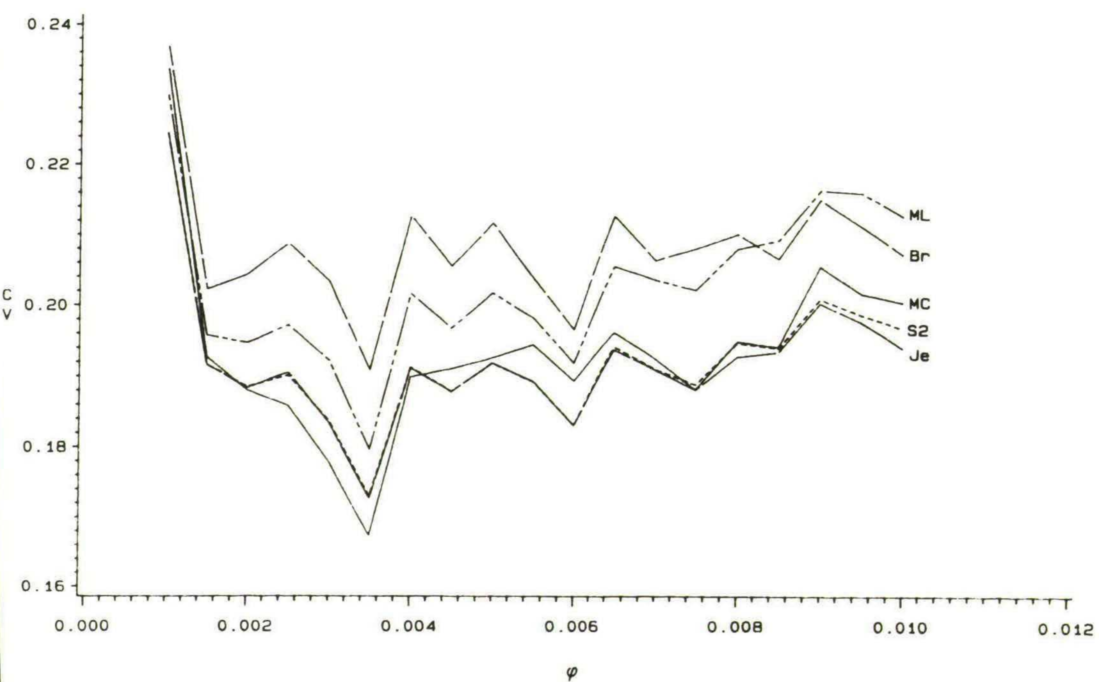


Figure 4a

φ^1=.001 φ^2=.01 p1=.15 p2=.70 d=3 m=7 n=6

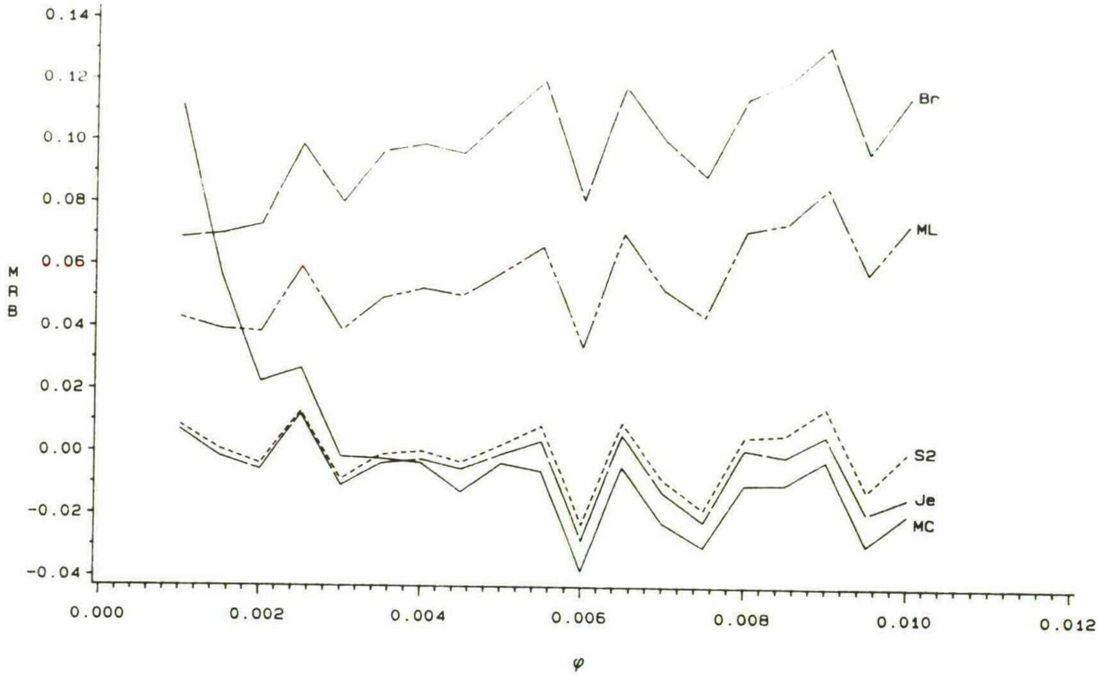


Figure 4b

φ^1=.001 φ^2=.01 p1=.15 p2=.70 d=3 m=7 n=6

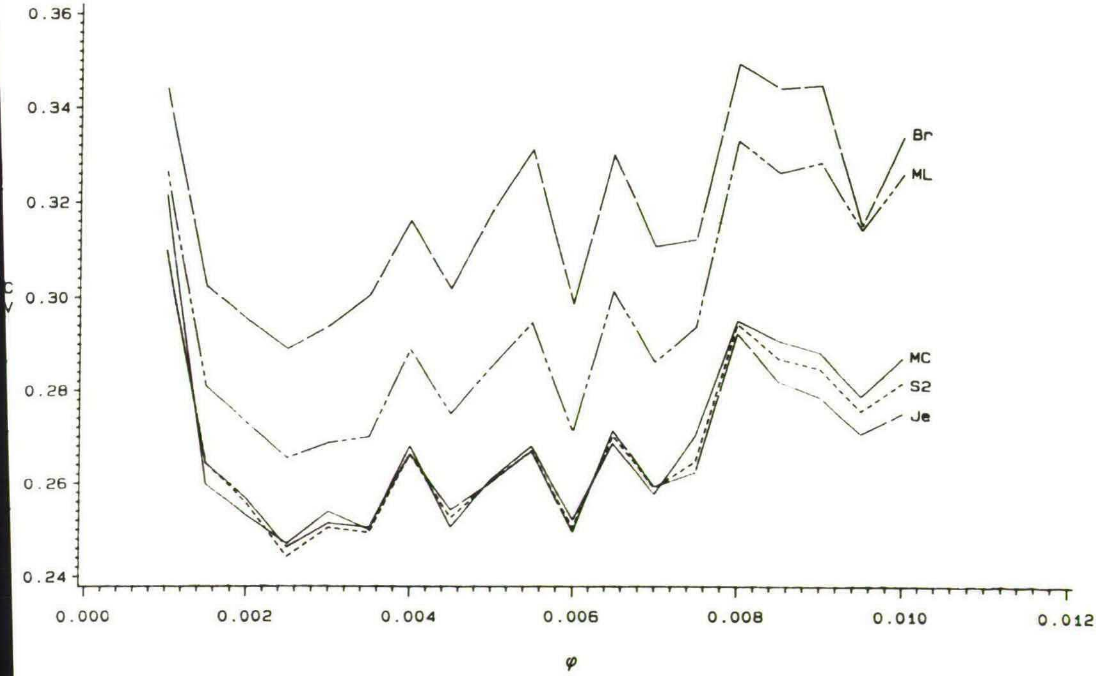


Figure 5a

$\varphi 1=.001$ $\varphi 2=.01$ p1=.15 p2=.70 d=3 m=7 n=12

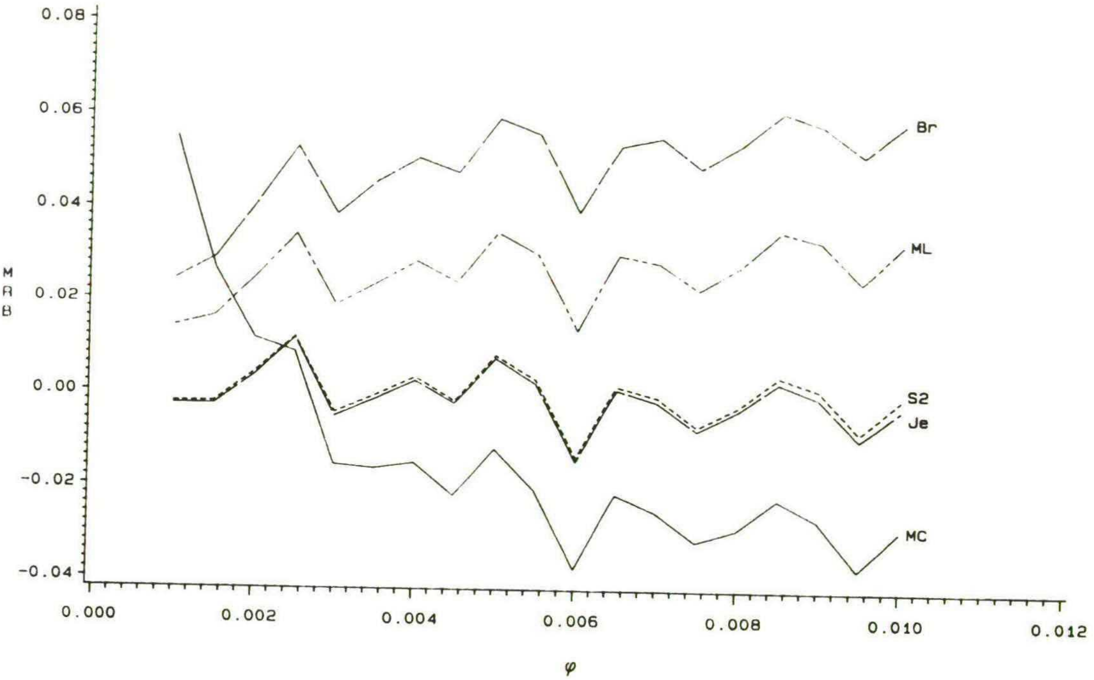
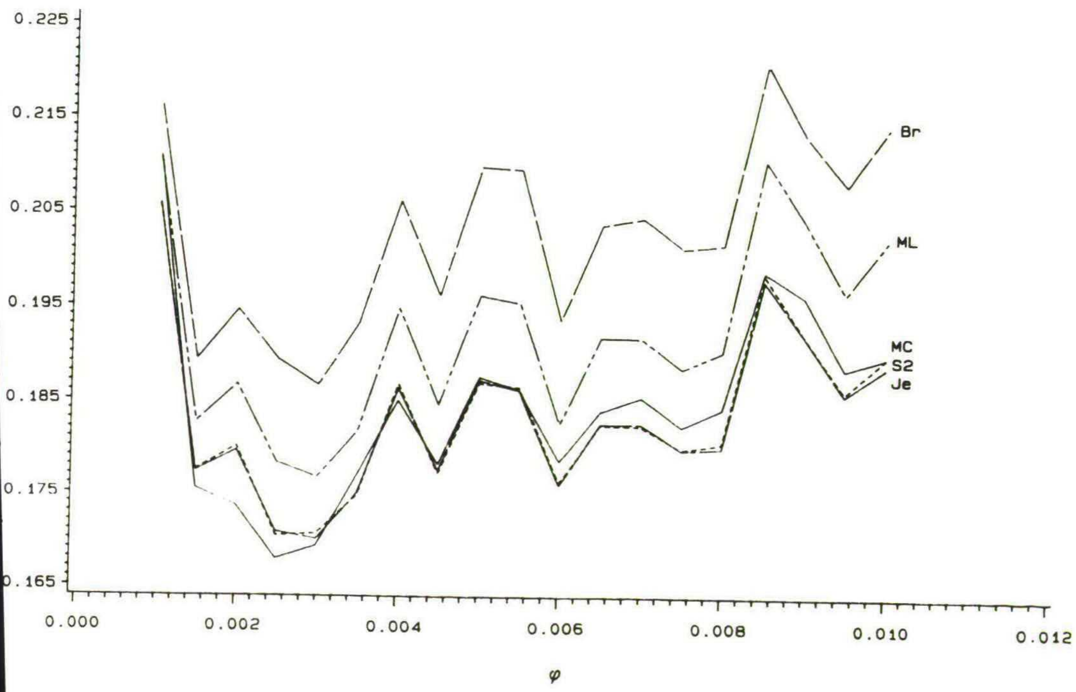


Figure 5b

$\varphi 1=.001$ $\varphi 2=.01$ p1=.15 p2=.70 d=3 m=7 n=12



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