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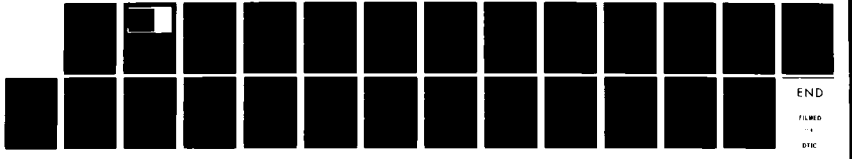

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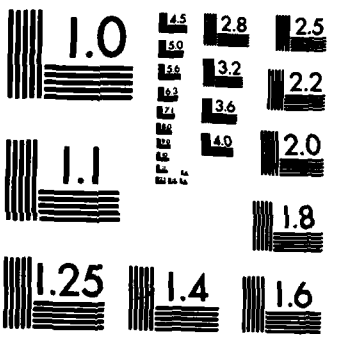

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AN INFERENTIAL APPROACH TO THE BIOASSAY DESIGN PROBLEM

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ABSTRACT

The Bioassay design problem may usefully be considered within an inferential framework, rather than by reference to a formal decision theoretic procedure based upon a number of special assumptions. Three graphical techniques are described to assist the user's selection of new design points. Firstly, a plot, against dose level, of the predictive probability of the death of the next rat will help the user to choose design points relating to particular regions of LD values; comparison with the maximum likelihood estimate of the response curve leads to informal stopping rules. Secondly, new approximations, to the posterior density of the effective dose, are proposed, for each LD value. These are related to the marginal likelihood ideas of Sprott and Kalbfleisch. Thirdly, mixtures of these densities leads to design measures for the distribution of future dose levels. These seem to make criteria like D-optimality rather tangential to the real design issue. The ideas are illustrated graphically by reference to a fertility example due to Bliss.

AMS (MOS) Subject Classification: 62P10, 62F15

Key Words: Bioassay, Design, Predictive distribution, Response curve, Posterior distribution of effective dose, Design measure, D-optimality.

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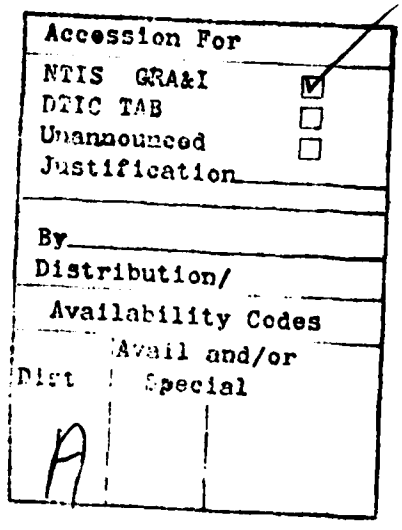
SIGNIFICANCE AND EXPLANATION

The bioassay design problem relates to a variety of practical solutions where there are zero-one responses which are regressed upon an explanatory variable. The problem addressed is "how do we choose the next few dose levels, given a few preliminary experiments?" Three graphical procedures are proposed including (i) a plot of the predictive response curve (ii) the posterior densities of effective doses for given design measures and (iii) a sensible choice of design measure which averages the posterior densities of the effective doses over LD values 1,...,99. A rat fertility experiment is analyzed to illustrate these procedures.



AN INFERENTIAL APPROACH TO THE BIOASSAY DESIGN PROBLEM

Tom Leonard

1. INTRODUCTION

Consider indicator variables $y_1,\ldots,y_n$ and explanatory variables $x_1,\ldots,x_n$, where y_i is one or zero, according to the death or survival for the ith rat, and x_i denotes the dose level for the ith. Having observed experiments on n rats suppose that we consider the design problem of how to choose the dose level x_{n+1} for the next rat.

Our practical procedures are based upon the following philosophy:

(a) The choice of x_{n+1} should be regarded as an inferential rather than a decision theoretic problem i.e. it would be useful to provide diagnostic devices giving guidelines on how x_{n+1} should be chosen, and permitting input from the user in relation to his experience and intuition. In particular, a graphical method summarizing the useful information in the data, rather then a formal decision, based upon special and possibly constrictive assumptions, will provide the user with a better understanding of what the data are trying to say.

(b) The more obvious features of the information in the data concerning the next design point x_{n+1} may be extracted by considering the probability of what is going to happen next, conditional upon what has already happened, and also conditional upon the various feasible choices of the design point. This may be represented by a graphical plot of the predictive probability

$$\phi(x_{n+1}) = \text{prob}(y_{n+1} = 1 | y_1,\ldots,y_n; x_1,\ldots,x_n; x_{n+1}) \quad \text{for } -\infty < x_{n+1} < \infty \tag{1.1}$$

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for the next indicator variable, conditional upon $(y_1,\ldots,y_n;x_1,\ldots,x_n)$, and the next design point x_{n+1}. Reference should be made here to Geisser (1971), who views the predictive distribution as summarizing the important information in the data concerning the next observation.

This graphical plot will be superior, for design purposes, to the maximum likelihood estimate of the response curve, since it takes account of variability of the parameter estimates. It may be used to clarify which dose levels will be useful design points for particular LD points of interest.

(c) The next level of complexity is to consider the posterior distributions of the effective doses for the LD points of interest since these indicate whether more experimentation is needed in order to be adequately precise about these regions of the response curve.

(d) Mixtures of the posterior distributions of the effective dose provide useful design measures which may be used to ascertain the scatter of the next few design points.

The technicalities of our approach will be Bayesian in spirit and the very simple methodology will provide a possible alternative to the full dress sequential Bayesian decision theoretic ideas of Freeman(1970). Existing non-Bayesian methods, well catalogued by Wetherill (1966), include the famous "up and down" method and the Robbins-Munro Process.

The philosophy outlined in this paper is also relevant to design problems for the linear statistical model. The latter requires rather different technicalities; it will be treated in detail elsewhere.

2. THE PREDICTIVE DESIGN METHODOLOGY

Consider the standard linear logistic model where $y_1, y_2, \ldots$ are independent, given corresponding probabilities $\theta_1, \theta_2, \ldots$, where θ_i denotes the probability that $y_i = 1$, and the logit parameters $\alpha_i = \log \theta_i - \log(1 - \theta_i)$ satisfy

$$\alpha_i = \beta_0 + \beta_1 x_i \quad (i = 1, \ldots, n) . \tag{2.1}$$

The predictive probability in (1.1) could be calculated by choosing a joint prior density for β_0 and β_1 and computing the expectation of $p(y_{n+1} = 1 | \beta_0, \beta_1) = \exp\{\beta_0 + \beta_1 x_{n+1}\}/(1 + \exp\{\beta_0 + \beta_1 x_{n+1}\})$ with respect to the corresponding joint posterior density of β_0 and β_1. This method involves two-dimensional numerical interpretations together with the specification of a prior. However, good approximations, when there is little prior information about β_0 and β_1, may be obtained by taking the posterior distribution of $\underset{\sim}{\beta} = (\beta_0, \beta_1)^T$, after n observations, to be bivariate normal with mean vector equal to the maximum likelihood vector $\hat{\underset{\sim}{\beta}} = (\hat{\beta}_0, \hat{\beta}_1)^T$ and covariance matrix $\underset{\sim}{C}_n$ equal to the inverse $\underset{\sim}{R}_n^{-1}$ of the likelihood information matrix

$$\underset{\sim}{R}_n = \sum_{i=1}^{n} n_i \hat{\theta}_i (1 - \hat{\theta}_i) \begin{pmatrix} 1 & x_i \\ x_i & x_i^2 \end{pmatrix} \tag{2.2}$$

where $\hat{\theta}_i = \exp\{\hat{\beta}_0 + \hat{\beta}_1 x_i\}/\{1 + \exp(\hat{\beta}_0 + \hat{\beta}_1 x_i)\}$ is the fitted maximum likelihood probability for the ith rat.

Hence, for any fixed x_{n+1}, the posterior distribution of $\alpha_{n+1} = \beta_0 + \beta_1 x_{n+1}$, given the first n observations, is approximately normal with mean vector $\xi_{n+1} = \hat{\beta}_0 + \hat{\beta}_1 x_{n+1}$, and variance

$$v_{n+1} = (\eta_{22} - 2x_{n+1}\eta_{12} + x_{n+1}^2\eta_{11})/(\eta_{22}\eta_{11} - \eta_{12})^2 \qquad (2.3)$$

where η_{jk} is (j,k)th element of the matrix in (2.2).

The predicted probability in (1.1) may therefore be approximated by

$$\phi^*(x_{n+1}) = \int_{-\infty}^{\infty} \frac{e^{\alpha}}{1 + e^{\alpha}} \psi(\alpha, \xi_{n+1}, v_{n+1}) d\alpha \qquad (2.4)$$

where the second term in the integrand is a normal density with mean ξ_{n+1} and variance x_{n+1}. Having obtained $\hat{\beta}$ and $\underset{\sim}{R}_n$ via a standard numerical optimization, ϕ^* may be calculated, for each fixed x_{n+1}, using a one-dimensional numerical integration. This result is exact, given the adequacy of the approximate posterior normality of β_0 and β_1, and will therefore be more accurate than standard asymptotic results for the expectations of nonlinear functions.

Note that the predictive probability $\phi(x_{n+1})$ approximated by (2.4), is also the posterior mean, after n observations, of $\theta_{n+1} = \exp\{\beta_0 + \beta_1 x_{n+1}\}/[1 + \exp\{\beta_0 + \beta_1 x_{n+1}\}]$, and ϕ is therefore the Bayes estimate of the response curve, under squared error loss. The posterior variance of θ_{n+1} may also be approximated, by

$$v(x_{n+1}) = \int_{-\infty}^{\beta} \left\{\frac{e^{\alpha}}{1 + e^{\alpha}} - \phi^*(x_{n+1})\right\}^2 \psi(\alpha, \xi_{n+1}, v_{n+1}) d\alpha \qquad (2.5)$$

and it is useful to plot the standard deviation $\sqrt{v}$ as a function of x_{n+1}, together with ϕ^*.

It is also useful to compare plots of ϕ^* and $\hat{\phi}$, where

$$\hat{\phi}(x_{n+1}) = \exp\{\hat{\beta}_0 + \hat{\beta}_1 x_{n+1}\}/\{1 + \exp(\hat{\beta}_0 + \hat{\beta}_1 x_{n+1})\} \qquad (2.6)$$

$$(-\infty < x_{n+1} < \infty)$$

The $\hat{\phi}$ function gives the limiting form as $n \to \infty$ of ϕ^* i.e. $\hat{\phi}$ and ϕ^* would be identical if β_0 and β_1 were known and equal to $\hat{\beta}_0$ and $\hat{\beta}_1$. For finite sample sizes ϕ^* allows for uncertainty about β_0 and β_1. Therefore, when plotted against x_{n+1}, the differences between the two curves ϕ^* and $\hat{\phi}$ express lack of information in the data about the actual response curve. Moreover, the curves may be close for some values of x_{n+1}, and very different for other values of x_{n+1}. This permits inferences about which LD values can be well investigated from the ϕ^* curve, given the previous design points. Note that the $\hat{\phi}$ curve is always steeper than the ϕ^* curve. The relative steepness provides a measure of the information in the data, for example if ϕ^* is very flat then this suggests that there is little information relating to any LD point.

Suppose, for example, that the user is particularly interested in obtaining a good estimate of the response curve for LD values between LD90 and LD99. Then the next dose level, or levels, could be selected to lie between the effective doses γ_{90} and γ_{99}, where in general $\phi^*(\gamma_p) = p/100$. He might continue to experiment, repeatedly using this selection scheme, until he is confident (e.g. according to the criteria discussed in the next paragraph) that his estimate of the response curve is reasonably accurate in the region of interest. This procedure should be regarded as inferential, since the user may modify it as necessary to take account of his intuition.

The graphical procedure outlined above permits a number of informal stopping rules. Suitable measures of the differences between the ϕ^* and $\hat{\phi}$ curves include (i) the area between the curves (ii) the area between the curves and the γ_{90} and γ_{99} dose levels, and (iii) the differences between γ_{90} and γ_{99} and the corresponding values $\hat{\gamma}_{90}$ and $\hat{\gamma}_{99}$ calculated from the $\hat{\phi}$ curve i.e. it is reasonable to stop when further observations would be

unlikely to affect those estimated LD points which are of interest to the user.

3. CHOOSING THE NEXT r DESIGN POINTS

As well as basing the inference for design upon the one-step ahead (myopic) predictive probabilities, it is in principle possible to consider the r-step ahead probabilities

$$\phi^*(y_{n+1},\ldots,y_{n+r}|y_1,\ldots,y_n;x_1,\ldots,x_{n+1}) = E_\beta^{(n)} \prod_{i=n+1}^{n+r} e^{\beta_0 y_i + \beta_1 x_i y_i}/(1 + e^{\beta_0 + \beta_1 x_i}) \tag{3.1}$$

where the expectation operator relates to the posterior distribution of β_0 and β_1, given $y_1,\ldots,y_n$ and $x_1,\ldots,x_n$. A possible approximation to ϕ^*, based upon standard results for approximating the expectation of a nonlinear function in terms of expectations and covariances, is

$$\hat{\phi} = \prod_{i=n+1}^{n+r} \Omega_i + \frac{1}{2}\Big(\prod_{i=n+1}^{n+r} \Omega_i\Big)^2 \sum_{i=n+1}^{n+r}\sum_{j=n+1}^{n+r} w(x_i,x_j)/\Omega_i\Omega_j \,. \tag{3.2}$$

where

$$\Omega_i = \{\phi^*(x_i)\}^{y_i}\{1 - \phi^*(x_i)\}^{1-y_i} \tag{3.3}$$

and the predictive covariance $w(x_i,x_j)$ of θ_{n+i} and θ_{n+j} may be computed, using two dimensional numerical integrations, from

$$w(x_i,x_j) = E_\beta^{(n)}\Big(\frac{e^{\beta_0 + \beta_1 x_i}}{1 + e^{\beta_0 + \beta_1 x_i}} - \phi^*(x_i)\Big)\Big(\frac{e^{\beta_0 + \beta_1 x_j}}{1 + e^{\beta_0 + \beta_1 x_j}} - \phi^*(x_j)\Big) \tag{3.4}$$

The expression in (3.1) is, after time n, a function of the r zero-one random variables $y_{n+1},\ldots,y_{n+r}$ and the future design points $x_{n+1},\ldots,x_{n+r}$. Therefore, for r larger than 2 or 3 it will be a bit too unwieldy to yield easy interpretations. However, a great deal of the information contained in this joint distribution is summarized by the predictive means $\phi^*(x_{n+1}),\ldots,\phi^*(x_{n+r})$ together with the predictive covariances in (3.4). When $i = j$ the latter include the predictive variances $v(x_{n+1}),\ldots,v(x_{n+r})$, obtained from (2.5).

It seems that not too much interpretable information would be wasted by just referring to the plots of the ϕ^* and $\sqrt{v}$ curves, already calculated for the one-step ahead design problem. Unless the user is confident in a special decision theoretic criterion which he wishes to combine with (3.1), we recommend that he does just this, but combined with the more detailed information contained in the posterior distributions of the effective doses, discussed in the next section. For example, if he is interested in obtaining good estimates of the effective doeses for the LD50, LD90, and LD99 points, then he could carry out further experiments for dose levels at the medians of those posterior distributions which seem insufficiently informative.

4. THE POSTERIOR DISTRIBUTION OF THE EFFECTIVE DOSE

Under the normal approximation to the posterior distribution of β_0 and β_1, as described in section 2, it is possible to use a standard Jacobian interpretation method to obtain the posterior density, after n observations, of the effective dose γ_p corresponding to the LD p point, for any p lying strictly between 0 and 100. This is evident since, with $\lambda = \log p - \log(100 - p)$, γ_p is expressible, in terms of β_0 and β_1, as

$$\gamma_p = (\lambda - \beta_0)/\beta_1 , \qquad (4.1)$$

The consequent approximate posterior density of γ_p is a complicated function of cumulative normal distribution functions. However, another, more interesting, approach is available by reference to the marginal likelihood procedures of Sprott and Kalbfleisch (1969).

In terms of the exact likelihood

$$\ell(\underset{\sim}{\beta}|\underset{\sim}{y},\underset{\sim}{x}) = \exp\{\beta_0 \sum_{i=1}^{n} y_i + \beta_1 \sum_{i=1}^{n} x_i y_i\} / \prod_{i=1}^{n} (1 + e^{\beta_0+\beta_1 x_i}) \tag{4.2}$$

of β_0 and β_1, the marginal likelihood of γ_p is defined to be

$$\tilde{\ell}(\gamma_p|\underset{\sim}{y},\underset{\sim}{x}) = \sup_{S_p} \ell(\underset{\sim}{\beta}|\underset{\sim}{y},\underset{\sim}{x}) \tag{4.3}$$

where

$$S_p = \{(\beta_0,\beta_1) : \gamma_p = (\lambda - \beta_0)/\beta_1\} \tag{4.4}$$

The expression if (4.3) may be calculated, for each fixed γ_p, by replacing β_1 in

$$\ell(\gamma_p,\beta_1|\underset{\sim}{y},\underset{\sim}{x}) \tag{4.5}$$

$$= \exp\{\lambda \sum y_i + \beta_1 \sum (x_i - \gamma_p)y_i\} / \prod [1 + \exp\{\lambda + \beta_1(x_i - \gamma_p)\}]$$

by the solution for β_1 to the conditional maximum likelihood equation

$$\sum_i (x_i - \gamma_p) \frac{e^{\lambda+\beta_1(x_i-\gamma_p)}}{1 + e^{\lambda+\beta_1(x_i-\gamma_p)}} = \sum_i (x_i - \gamma_p)y_i \tag{4.6}$$

which may be solved iteratively, using Newton-Raphson. Note that the solution for β_1 is a function of γ_p. Therefore substitution for β_1 in (3.5) will affect this expression as a function of γ_p. This means that the marginal likelihood will be a non-obvious function with a wider spread than obtained by replacing β_1 by its unconditional maximum likelihood estimate $\hat{\beta}_1$.

Leonard (1982a) describes a general result, under wide regularity conditions, which shows that the marginal posterior density of a parameter, under an uninformative prior, is well approximated by its marginal likelihood when the latter is normalized to integrate to unity. The approximation is indeed almost exact, in a variety of special cases. Therefore the expression in (4.3) may be viewed as approximately proportional to the marginal posterior density of γ_p. This is useful, since γ_p may now be estimated, say, by its posterior median, as an alternative to the maximum likelihood estimate, and approximate posterior probability statements may be made about γ_p.

Leonard gives a refinement to this approximation, which may be justified by approximating the marginalization of the joint posterior density of γ_p and β_1, using the first term in an Edgeworth expansion. Hence we propose approximating the marginal posterior density of γ_p by

$$\pi^*(\gamma_p|\underset{\sim}{\chi},\underset{\sim}{x}) \propto \left\{ \sum_i (x_i - \gamma_p)^2 \frac{e^{\lambda+\tilde{\beta}_1(x_i-\gamma_p)}}{\left[1 + e^{\lambda+\tilde{\beta}_1(x_i-\gamma_p)}\right]^2} \right\}^{-1/2} \tilde{\ell}(\gamma_p|\underset{\sim}{\chi},\underset{\sim}{x}) \qquad (4.7)$$

where $\tilde{\ell}(\gamma_p|\underset{\sim}{\chi},\underset{\sim}{x})$ is the marginal likelihood and $\tilde{\beta}_1$ is the solution for β_1 to (3.6). The adjustment term in (3.7) is based upon the second derivative of the log of the expression in (3.5).

Whilst the density in (3.7) is easy enough to compute, a more explicit approximation is available; this will be a bit less accurate numerically. Consider the multivariate normal approximation

$$\ell^*(\underset{\sim}{\beta}|\underset{\sim}{\chi},\underset{\sim}{x}) = \ell^*(\hat{\underset{\sim}{\beta}}|\underset{\sim}{\chi},\underset{\sim}{x}) \exp\{-\tfrac{1}{2}(\underset{\sim}{\beta} - \hat{\underset{\sim}{\beta}})^T \underset{\sim}{R}_n (\underset{\sim}{\beta} - \hat{\underset{\sim}{\beta}})\} \qquad (4.8)$$

where $\hat{\underset{\sim}{\beta}} = (\hat{\beta}_0, \hat{\beta}_1)^T$ is the standard maximum likelihood estimator of $\underset{\sim}{\beta}$, and $\underset{\sim}{R}_n$ is the information matrix in (2.2). Under this approximation the marginal likelihood in (3.3) and the density in (3.10) may be respectively replaced by

$$\ell^*(\gamma_p|\underset{\sim}{y},\underset{\sim}{x}) \propto \exp\{-\tfrac{1}{2}(\hat{\beta}_0 + \hat{\beta}_1\gamma_p - \lambda)^2/(c_{22}\gamma_p^2 + 2c_{11}\gamma_p + c_{11})\} \qquad (4.9)$$

and

$$\pi^*(\gamma_p|y,\underset{\sim}{x}) \propto (c_{22}\gamma_p^2 + 2c_{12}\gamma_p + c_{11})^{-\frac{1}{2}}\,\ell^*(\gamma_p|\underset{\sim}{y},\underset{\sim}{x}) \qquad (4.10)$$

where c_{jk} is the (j,k)th element of the inverse of R_n. These results illustrate specific functional forms in terms of γ_p.

Note however the interesting point that, whilst the tails of the approximating function in (4.10) will quickly become negligibly close to zero as $|\gamma_p|$ becomes large, the functions will not theoretically possess finite integrals over $-\infty < \gamma_p < \infty$, since they will ultimately behave like a constant times $|\gamma_p|^{-1}$ as $|\gamma_p| \to \infty$. This phenomenen is illustrated by the thick tails in Figure 3. If the Jacobian/integration method indicated in the first paragraph of this section had been performed then the tails would instead be Cauchy-like, owing to the normal random variable in the denominator of (4.1). If the exact (logistic) likelihood of β_0 and β_1 was employed, together with non-informative uniform priors for β_0 and β_1 then the tails of the exact marginal posterior density of γ_p would be slightly thinner than Cauchy, and, like the Cauchy, would possess a finite integral over $-\infty < \gamma_p < \infty$. For the approximation in (4.10) it would therefore seem reasonable to down weight the tails after a certain point. In most numerical examples, the situation will be so clear cut that it will be adequate to do this graphically. For example, for the posterior density of the medium effective dose in Figure 3, it would seem reasonable to down weight the tails outside the interval (0.15, 0.4) in such a fashion that they become virtually equal to zero at $\gamma_p = 0.05$ and $\gamma_p = 0.5$.

5. RELATED WORK

Ramsay (1972) and Disch (1981) describe a non-parametric Bayesian approach where the prior distribution of the derivatives of the whole response curve is assumed to follow a Dirichlet process. This yields a posterior estimate for the response curve which is a weighted average of a step function and a prior estimate. It would be possible to calculate the predictive probability using their prior assumptions. Alternatively Leonard (1978, 1982b) describes a Gaussian prior distribution across function space for a logistic transform; his non-parametric smoothing procedure could also be adapted to this situation.

For design purposes, it seems easier to employ the simple parametric assumption in (2.1). This yields an analysis, free from choice of prior parameter, and giving a continuous estimate of the response curve. For example, Disch attempts to obtain the posterior distribution of the effective dose, and runs into substantial technical problems, whereas the approximate densities in (3.7) and (3.9) are much easier to calculate.

In practical terms, a substantial amount of zero-one data would be needed to dispute the parametric form in (2.1). Moreover, it would, in such circumstances, be possible to use a slightly more general parametric from e.g. permitting skewness, or thicker tails, before proceeding to a full-dress non-parametric Bayesian approach. I view non-parametric Bayes as useful for investigating a hypothesized model when a moderate amount of data has been collected; for design problems and less complete amounts of data, a previously established parametric form will probably work better.

6. NUMERICAL EXAMPLE

The data in Table 1 were introduced by Bliss (1952, p. 540) indicate the fertility or non-fertility of 57 rats each of which as been subjected to one of five dose levels of a drug. The dose levels are described as fractions of 25 milligrams.

Table 1: Fertility Experiment for 57 Rats

Dose level	0.15	0.20	0.25	0.3	0.4	0.6
No. of Rats	5	10	10	10	11	11
No. of Fertile Rats	0	2	4	8	11	11

The curves in Figure 1 relate to the first three dose levels only, whilst Figures 2 and 3 are based upon the whole data set.

The ϕ^* curve in Figure 1 differs substantially from the $\hat{\phi}$ curve suggesting that more data needs to be collected. When choosing the next design point, suppose, for example, that the main interest lies in LD points above the LD90 point. Then the ϕ^* curve suggests that the design point should be chosen above 0.47, a substantially different recommendation than the value of 0.44 suggested by the cruder $\hat{\phi}$ curve. If interest lay in the LD99 point then the low trajectory of the ϕ^* curve suggests that substantially more data needs to be collected. It seems reasonable to start off with several more design points, between about 0.6 and 0.8. The ϕ^* curve and $\hat{\phi}$ curve are closest together for design points between 0.20 and 0.27 and the standard deviation of ϕ^* dips at this point. This suggests that the previously chosen design points 0.15, 0.20, and 0.25 are best for investigating LD points just above the LD20 point, and that future design points will need to be more widely dispersed if it is required to get a good estimate of the whole curve. If for example, interest lies in the whole curve

between the LD10 point and LD90 point then future design points should be scattered between 0.11 and 0.47. Therefore the ϕ^* curve effectively defines the scale on which the design points should be chosen.

Moving on to Figure 2, we see that with the increased information the ϕ^* curve is closer to the $\hat{\phi}$ curve. Given experience with the method the remaining differences would help us to judge how much more data is needed before we would be able to stop the experiment on the grounds that ϕ^* and $\hat{\phi}$ are close enough for our purposes. At the moment the curves seem just about close enough to stop if we are only interested in good estimates between the LD10 point and the LD90 points. For the ϕ^* and $\hat{\phi}$ curves these LD points correspond to design points within the respective ranges (0.16, 0.37) and (0.17, 0.36) which are fairly close. However, if, say, interest lay in the LD99 point then it seems better to collect more data; the ϕ^* and $\hat{\phi}$ curves now yield effective doses of 0.54 and 0.47, which are more discrepant.

Once the quantity of data collected gives us reasonable accuracy then it is useful to look more closely at the posterior distributions of various effective doses, in order to substantiate any inferences drawn from the predictive curve. The densities in Figure 3 correspond to the LD50, LD90, and LD99 points. As we move from left to right we see that the curves become progressively more flat and progressively more skew. For a given required degree of accuracy they tell us which effective doses can be accurately estimated from the present data. The spread of the densities gives us some idea of what proportions of future design points should be placed at different LD points of interest.

In summary, we feel that the curves in Figure 1,2, and 3 provide the user with most of the information necessary to make suitable inferences about future design points. A formal analysis based upon special assumptions would

conceal much of this information and, whilst giving conditional optimality, would restrict the user from making a practically reasonable choice of design point.

7. A SENSIBLE CHOICE OF DESIGN MEASURE

Bioassay design problems are of course very different from design problems for the linear statistical model, where the optimal design points tend to stick to the boundary of the design space. An obvious design measure in the present nonlinear situation could be based upon a prespecified weight function $w(p)$ indicating the relative importance of LD points $1,2,\ldots,99$, where $\sum w(p) = 1$. The derivative of our recommended design measure is then the mixture

$$\tau(\gamma|\underset{\sim}{\chi},\underset{\sim}{x}) = \sum_{p} \pi_p(\gamma|\underset{\sim}{\chi},\underset{\sim}{x})w(p) \qquad (7.1)$$

where π_p is the posterior density of the effective dose γ_p. Areas under the curve in (5.1) should be taken to indicate the proportions of future design points which should be placed in the corresponding dose level regions. The user may find (5.1) to be a useful, though slightly more formal diagnostic aid. For example, if he views the importance of the LD50, LD90 and LD99 points as roughly equal, and no other LD point to be of interest, then he should average the curves in Figure 3 and place his design points accordingly. As the average curve is a density there will be no problems with any boundary of the design space. The user should stop sampling when the curve in (6.1) is sufficiently spiked, at those p for which $w(p) > 0$, to guarantee accurate enough estimation of the effective doses.

Consider now the situation where there is no special preference for particular design points and the objective of the experiment is to simply obtain a reasonable estimate for the whole response curve. In this case the choice, $w(p) = 1/99$ for all p, seems appropriate. The design curve in Figure 4 makes this assumption for the data in Table 1. Note from Figure 3 that the median of the curve in Figure 4 is close to the posterior median of the median effect dose. The design curve is of course more spread out than the posterior density of the median effective dose.

We propose this choice of the weights $w(p)$ as leading to a reasonably objective design measure which should be appropriate in a wide range of situations. Rather than being developed from an optimality criterion it can be justified purely by thinking in terms of probability i.e. (i) for a particular LD point π_p is the obvious design measure, since dose levels chosen according to this measure will have the best change of covering the LDp part of the curve (ii) if we want there to be an equal chance of the selected dose levels covering LD points $1,\ldots,99$ then the uniform mixture of the π_p's is clearly appropriate; if we do not want this then the mixing probabilities should be adjusted accordingly. In our opinion, criteria like D-optimality can only serve to confuse the issue.

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REFERENCES

Bliss, C. I. (1952). The Statistics of Bioassay. Academic Press.

Disch, D. (1981). Bayesian non-parametric inferences for effective doses in a quantal experiment. Biometrics 37, 713-722.

Freeman, P. R. (1970). Optimal sequential estimation of the median effective dose. Biometrika 57, 79-81.

Geisser, S. (1971). The inferential use of predictive distribution. Formulations of Statistical Inference, ed. by Godembe and Sprodt. Toronto: Holt, Rinehart and Winston, pp. 456-466.

Leonard, T. (1978). Density Estimation, Stochastics, Processes, and Prior Information (with Discussion). J. Roy. Statist. Soc. B. 46, 113-146.

_____ (1982a). Comment on the paper by Lejeune and Faulkenberry. J. Amer. Statist. Assoc. (June issue, to appear)

_____ (1982b). An empirical Bayesian approach to the smooth estimation of unknown functions. University of Wisconsin, Mathematics Research Center, Technical Report No. 2339.

Ramsey, F. L. (1972). A Bayesian approach to bioassay. Biometrics 28, 841-848.

Sprott, D. A. and Kalbfleish, J. D. (1969). Examples of likelihoods and comparison with point estimations and large sample approximations. J. Amer. Statist. Assoc. 64, 465-484.

Wetherill, G. B. (1966). Sequential methods in statistics. Methuen.

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FIGURE 1. PREDICTIVE CURVES FOR DATA AT FIRST 3 DOSE LEVELS

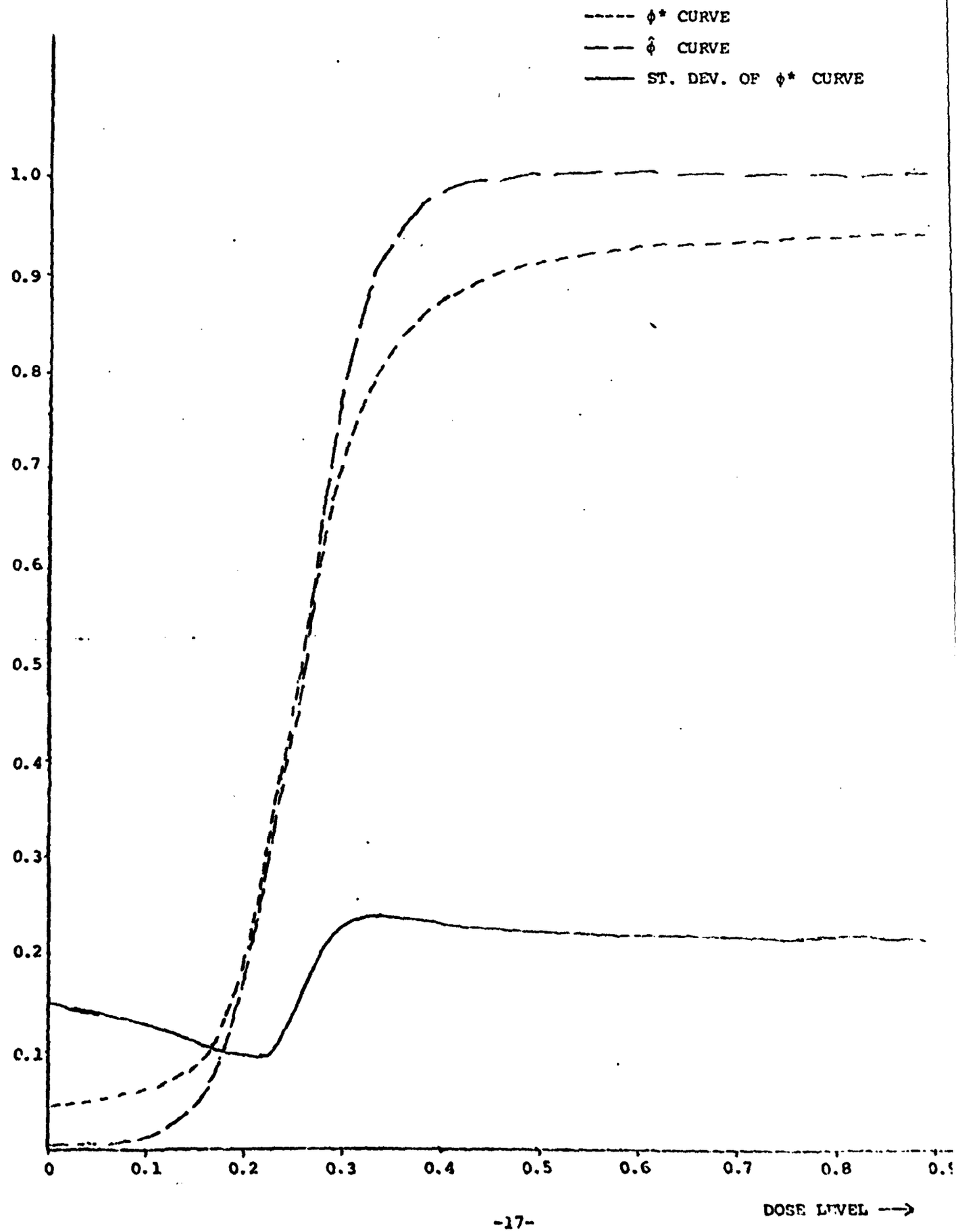


FIGURE 2: PREDICTIVE CURVES FOR FULL DATA SET

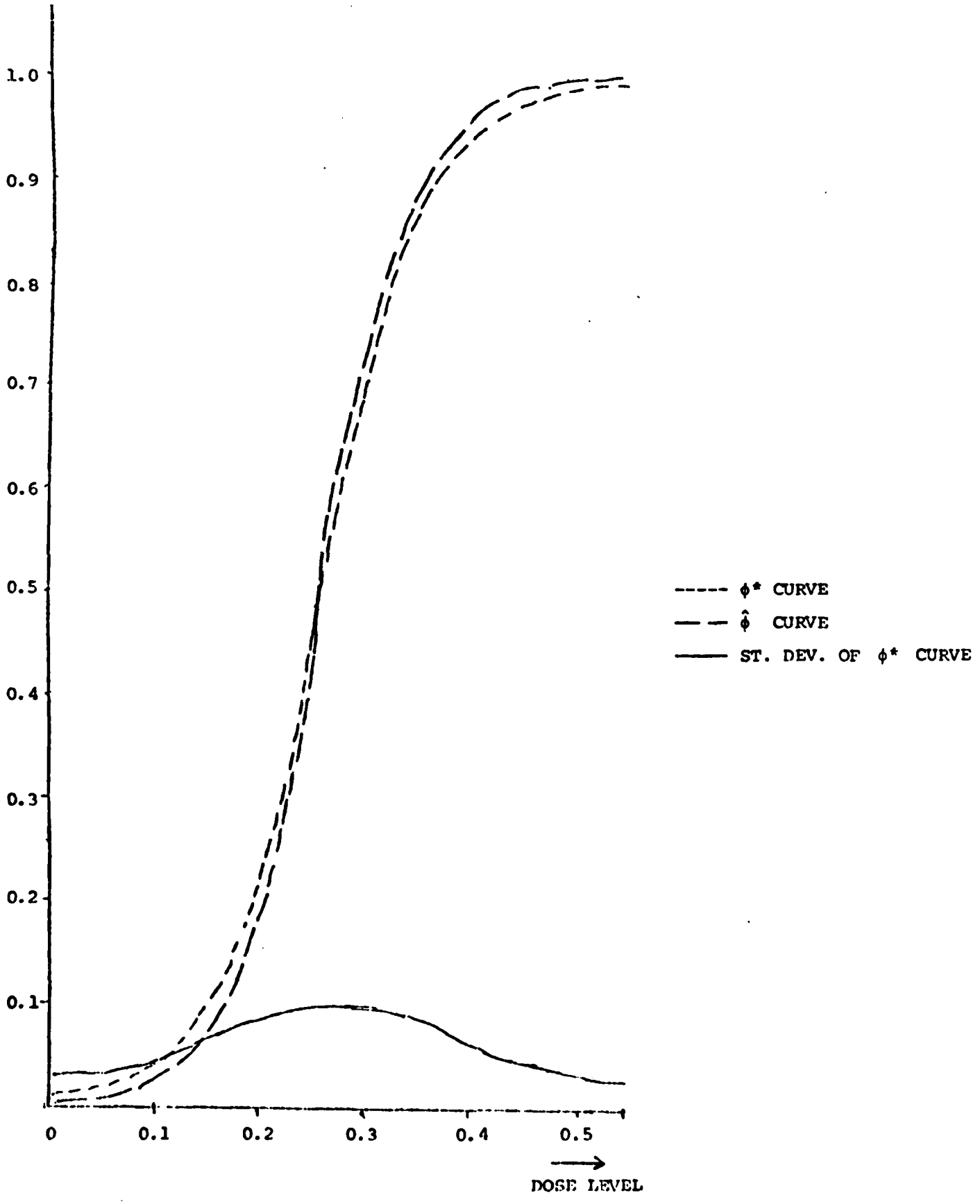


FIGURE 3: APPROXIMATE POSTERIOR DENSITIES OF EFFECTIVE DOSES AT LD 50, LD 90, AND LD 99 POINTS

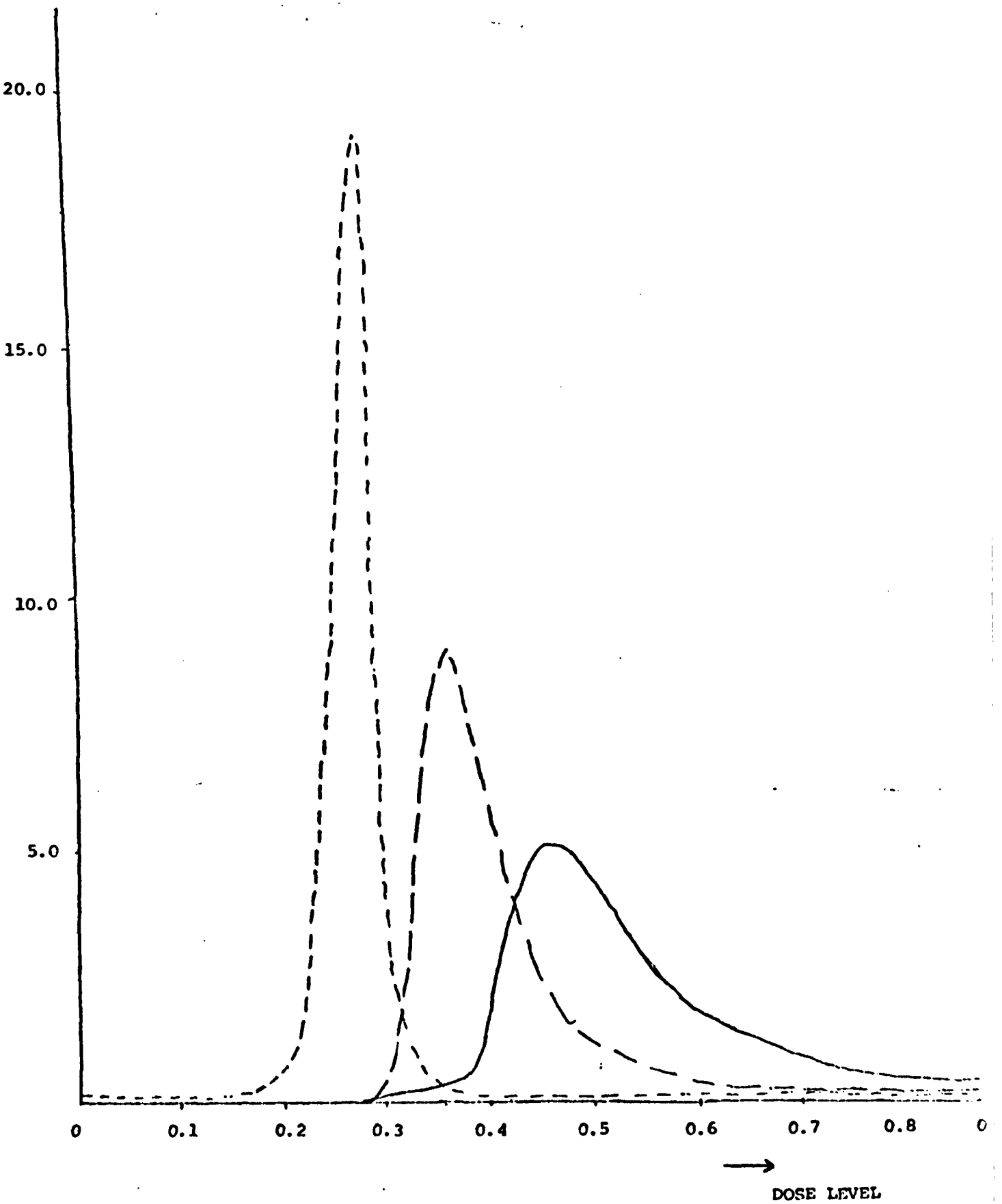
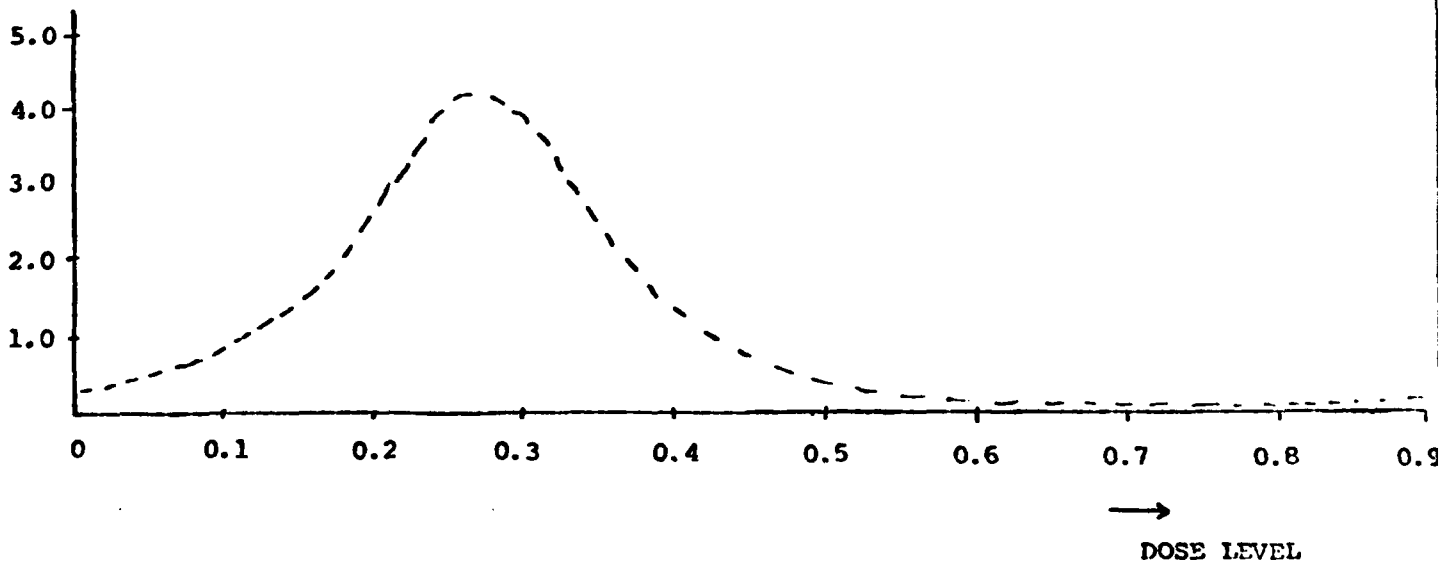


FIGURE 4: PLOT OF DERIVATIVE OF DESIGN MEASURE



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The Bioassay design problem may usefully be considered within an inferential framework, rather than by reference to a formal decision theoretic procedure based upon a number of special assumptions. Three graphical techniques are described to assist the user's selection of new design points. Firstly, a plot, against dose level, of the predictive probability of the death of the next rat will help the user to choose design points relating to particular regions of LD values; comparison with the maximum likelihood —
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ABSTRACT (cont.)

estimate of the response curve leads to informal stopping rules. Secondly, new approximations, to the posterior density of the effective dose, are proposed, for each LD value. These are related to the marginal likelihood ideas of Sprott and Kalbfleisch. Thirdly, mixtures of these densities leads to design measures for the distribution of future dose levels. These seem to make criteria like D-optimality rather tangential to the real design issue. The ideas are illustrated graphically by reference to a fertility example due to Bliss.