Optimal Experimental Design Strategies for Detecting Hormesis

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June 10, 2010

Abstract

Hormesis is a widely observed phenomenon in many branches of life sciences ranging from toxicology studies to agronomy with obvious public health and risk assessment implications. We address optimal experimental design strategies for determining presence of hormesis in a controlled environment using the recently proposed Hunt-Bowman model. We propose alternative models that have an implicit hormetic threshold, discuss their advantages over current models, construct and study properties of optimal designs for (i) estimating model parameters, (ii) estimating the threshold dose, and (iii) testing for the presence of hormesis. We also determine maximin optimal designs that maximize the minimum of the design efficiencies when we have multiple design criteria or there is model uncertainty where we have a few plausible models of interest. We apply our optimal design strategies to a teratology study and show our proposed designs outperform the implemented design by a very wide margin for many situations.

KEY WORDS: continuous design, dose-response, Hunt-Bowman model, logistic model, maximin design, quadratic-logistic model, weibull model

1 Introduction

Hormesis is a dose-response relationship which is characterized by low dose stimulation (beneficial effect) and high dose inhibition (destructive intoxication). Hormetic effects mean that there might actually be a reduced risk of exhibiting toxic effects at low exposure levels. Hormetic effects are observed in pharmacology (Hardman, Limbird and Gilman, 2001), toxicology (Eaton and Klaassen, 2001; Hayes, 2001) and radiation experiments (Calabrese and Baldwin, 2002). Calabrese and Baldwin (2003) reported that hormetic effects are also observed in non-toxicological fields: experimental psychology, plant biology and chemotherapy. In such areas, hormetic effects may mean enhanced longevity or decreased disease incidence. The presence of hormesis was clearly shown in Haseman (1983), where a reduction in the background tumor incidence was observed in an analysis of 25 cancer studies in the National Toxicology Program.

Hormesis implies the existence of a threshold dose level which is defined as the maximum nonzero exposure level below which no adverse events above background response occur. In particular, the background response occurs at this threshold dose level. This definition is widely accepted, see for example, Hunt and Bowman (2004), Hatch (1971), Cox (1987). However, despite the wide spread existence of hormesis and discussion in scientific circles, the subject of hormesis is not without controversy, see Thayer et al. (2006), Cook and Calabrese (2006a, 2006b), for example.

Hunt and Bowman (2004) characterized the overall dose-response relationship by a piecewise function that consists of a quadratic u-shape curve at dose levels that are lower than the threshold and a shifted logistic curve at dose levels that are higher than the threshold. The Hunt-Bowman model has advantages over several threshold models but retains two drawbacks common to many threshold models; the derivative is not continuous at the hormesis threshold dose level and the u-shape is symmetric at low dose levels. To overcome the disadvantages, we propose smooth analytic models that do not possess the threshold dose level parameter explicitly. Specifically, we model the overall dose-response relationship by a sum of an exponential decay and a sigmoidal curve that may include, for example, the logistic or Weibull curve.

There are many papers in various disciplines that discuss the existence and estimation issues for a threshold model. Some examples are Pastor and Guallar (1998), Ulm (1991), Slob (1999), Goetghebeur and Pocock (1995), and Rodricks (2003), to name a few. However, optimal experimental strategies for detecting hormesis have not been studied. We believe that this paper is the first serious attempt to address design issues for detecting hormesis in an experiment using a variety of techniques. Our study focusses on locally optimal designs where we assume nominal values of the model parameters are available. These optimal designs typically require the least effort to find and usually represents a first step in searching for more complicated designs later on. Specifically, we construct locally optimally designs for (i) estimating model parameters, (2) estimating the threshold and (3) testing presence of hormesis. Because optimal designs can perform inefficiently under another criteria, it is desirable to have

designs that are robust under a variation of criteria, see for example, Wong (1994) and Moerbeek (2005). To this end, we also construct maximin optimal designs that maximize the minimal efficiency across the multiple criteria. The resulting maximin optimal design provides some assurance that the design can deliver reasonable efficiencies for a few optimality criteria at the same time. We also provide similar applications of maximin optimal designs to the situations when there is uncertainty in the model assumptions and we wish to design for a few plausible models at the same time.

2 Approximate Design and Design Criteria

An experimental design ξ is a discrete probability measure defined on a pre-selected dose interval $\Omega = [0, \bar{d}]$. We denote such a design by ξ=$\{d_0, d_1, \ldots, d_k; w_0, w_1, \ldots, w_k\}$, where k is the number of distinct doses and $d_i \in \Omega = [0, \bar{d}]$. The weights w_i are non-negative numbers that sum to unity and w_i represents the relative proportion of the total number of observations allocated to the i^{th} dose, $i = 1, 2, \ldots, k$. In practice, if N is the pre-determined sample size for the study, the number of animals allocated to dose d_i is $Nw_i, i = 1, \ldots, k$, subject to $Nw_0 + Nw_1 \cdots + Nw_k = N$. Such designs are frequently referred to as continuous designs. They are easier to find and study than exact designs (Kiefer, 1959). The design problem is to find the optimal number of dose levels (k), where these doses (d_i's) are and what proportion (w_i's) of observations to take at each of these doses.

Given a model with mean response function μ, the threshold dose level is the maximum nonzero exposure level below which no adverse events above the background response occur and there is the background response at this level, that is

$$\tau = \tau(\theta) = \max\{\, d \in \Omega \,:\, \mu(d, \theta) \leq \mu(0, \theta)\}.$$

Let $\hat{\tau}$ be the least squares estimator (LSE) of τ. The optimality criterion for the most precise estimation of the threshold level requires us to minimze $\mathrm{Var}(\hat{\tau})$ over all continuous designs on Ω. By the δ-method we have that $\mathrm{Var}(\hat{\tau})$ is approximately proportional to $b^T(\theta)M^{-1}(\xi, \theta)b(\theta)$, where

$$M(\xi, \theta) = \sum_i f(d_i, \theta) f^T(d_i, \theta) w_i, \quad f(d, \theta) = \frac{\partial}{\partial \theta}\mu(d, \theta), \quad b(\theta) = \frac{\partial}{\partial \theta}\tau(\theta).$$

The matrix $M(\xi, \theta)$ is the information matrix obtained from design ξ for θ in the model

$$y_j = \mu(d_j, \theta) + \varepsilon_j$$

where the $y_j's$ are outcomes and errors $\varepsilon_j's$ are independently identically distributed random values with zero mean and finite variance. Designs with a singular information matrix are called singular designs. Such designs do not permit all parameters in the models to be estimated.

Following convention (Silvey, 1980, Pukelsheim, 1993), our design criteria are formulated as functions of the information matrix. For a nonlinear model, the information matrix depends on the model parameters that we want to estimate. Consequently, nominal values of the parameters are required to construct an optimal design. Typically nominal values come from experts' opinion or results from similar experiments. Once nominal values for the model parameters are available, we assume that they are true values of the model parameters so that the information matrix is now free of unknown parameters. Upon optimization, we obtain an optimal design, which we use to produce the next set of estimates for the model parameters. Usually, these estimates stabilize after a few iterations and the optimal design does not change anymore. These locally optimal designs are easier to find and they usually form the basis for constructing designs that are more robust to model assumptions or designs that can meet the multiple objectives in the study, see Section 2.3 and Section 4.

There are a few design criteria for studying hormesis. If we are interested in the precise estimation of the threshold dose level, an appropriate design is a locally τ-optimal design that minimizes $b^T(\theta)M^{-1}(\xi,\theta)b(\theta)$ where $b(\theta)$ is given near the definition of the information matrix. This criterion is a particular case of the widely used c-optimality criterion discussed in design monographs (Silvey, 1980, Pukelsheim, 1993). For our purpose here, we take $c = b(\theta)$. For estimating model parameters in the mean function, D-optimality is appropriate. A D-optimal design minimizes the volume of the confidence ellipsoid for the parameter θ and so we have the most precise estimates of the parameters. Techniques for finding c and D-optimal designs are well known and are described in design monographs mentioned above.

A more challenging design question is how to design a study specifically for detecting the existence of hormesis. Depending on the context, hormesis may exhibit a J-shaped, U-shaped or an inverted U-shaped dose response, see Rodricks (2003) for details. We assume that the mean response as a function of the dose is differentiable and to fix ideas, assume that when hormesis exists, its derivative is negative at the zero dose and nonnegative otherwise. Consequently, the hypothesis for the existence of hormesis is

$$H_0 \,:\, \mu'(0,\theta) \geq 0 \quad \text{vs} \quad H_1 \,:\, \mu'(0,\theta) < 0$$

where $\mu'(d,\theta) = \partial\mu(d,\theta)/\partial d$. An optimal design that maximizes the power of hypothesis testing is a design that minimizes $\text{Var}(\mu'(0,\hat{\theta}))$. By the δ-method, we have

$$\text{Var}(\mu'(0,\hat{\theta})) \approx h^T(0,\theta)M^{-1}(\xi,\theta)h(0,\theta)$$

where $h(d,\theta) = \partial f(d,\theta)/\partial d$. This implies that we want a locally optimal design that minimizes $h^T(\theta)M^{-1}(\xi,\theta)h(\theta)$ where $h(\theta) = h(0,\theta)$. This criterion is also a special case of c-optimality and for convenience, we call the criterion h-optimality and designs that minimize the criterion h-optimal. Because these designs minimize the variance of the estimate of the derivative of the mean response at 0, they remain optimal for detecting other types of hormesis when we reverse the null and alternative hypotheses.

Throughout, we measure the worth of a design by its efficiency. This number is between 0 and 1 and is typically the ratio of the criterion values from the current design and the optimal design and reported as a percentage after multiplying by 100%. A design with 50%-efficiency means that it has to be replicated twice to do as well as the optimal design. For D-efficiency, we work with the p-root of the ratio to maintain this interpretation, where p is the number of parameters of interest.

In the next section, we focus on the Hunt-Bowman model and construct a variety of optimal designs for the model. In Section 4, we propose alternative models that do not have explicit threshold parameter and present a variety of optimal designs for these models. Robust designs are discussed in Section 5. These designs ensure the constructed designs have the best possible efficiencies under various design criteria or different model assumptions. Justifications for all the optimal designs are quite similar and we sketch the key ideas in Lemma 1 and Lemma 2 in the appendix.

3 The Hunt-Bowman Model

Hunt and Bowman (2004) proposed modeling the mean response $\mu(d)$ at dose d using the piecewise quadratic-logistic function

$$\mu(d) = \mu(d, c_1, \tau, \beta_0, \beta_1) = \begin{cases} c_1 d^2 + c_2 d + \kappa & 0 \le d \le \tau \\ \frac{1}{1+e^{\beta_0 - \beta_1 (d-\tau)}} & d \ge \tau \end{cases} \tag{1}$$

with two restrictions on the six parameters $c_1, c_2, \kappa, \tau, \beta_0, \beta_1$: $\mu(0) = \mu(\tau)$ and $\mu(\tau-) = \mu(\tau+)$. The former follows from the definition of the hormesis threshold and the latter follows from the continuity of the dose-response curve. These restrictions imply $\kappa = \frac{1}{1+e^{-\beta_0}}$ and $c_2 = -c_1\tau$. The parameter τ is the threshold dose and the vector of model parameters for the Hunt-Bowman model is $\theta = (c_1, \tau, \beta_0, \beta_1)^T$ with 4 independent parameters. Here and throughout, $\mu(d)$ is the mean response at dose d and sometimes, we write the mean response as $\mu(d, \theta)$ to emphasize its dependence on θ.

Hunt and Bowman (2004) used model (1) to fit data from a study that measured developmental effects of the chemical diethylhexyl phthalate on mice. In the experiment, the pregnant animals were exposed to one of five dose levels including the control dose at $d = 0$. Here, a dose level corresponds to administering the drug as a percentage of the animal's diet. The number of affected fetuses was recorded for each animal and analysis results from Hunt and Bowman (2004) showed a u-shape dose response at low dose levels. Figure 1 in Section 4 shows the mean function of the Hunt-Bowman model for various sets of values for θ and also the fitted mean response function from the exp+log model to be discussed.

3.1 Locally Optimal Designs for the Hunt-Bowman model

We now investigate the locally τ-optimal design, the locally D-optimal design and the locally h-optimal design for the Hunt-Bowman model. If $\theta = (c_1, \tau, \beta_0, \beta_1)^T$, a direct

calculation shows the regression vector $f(d,\theta)$ for the model is

$$f(d,\theta) = \begin{cases} \left(d^2 - \tau d, -c_1 d, -\frac{e^{\beta_0}}{(1+e^{\beta_0})^2}, 0\right)^T & 0 \le d \le \tau, \\ \left(0, -\beta_1 \frac{e^{\beta_0-\beta_1(d-\tau)}}{(1+e^{\beta_0-\beta_1(d-\tau)})^2}, -\frac{e^{\beta_0-\beta_1(d-\tau)}}{(1+e^{\beta_0-\beta_1(d-\tau)})^2}, \frac{(d-\tau)e^{\beta_0-\beta_1(d-\tau)}}{(1+e^{\beta_0-\beta_1(d-\tau)})^2}\right)^T & d \ge \tau. \end{cases}$$

Table 1 shows the locally D-optimal design constructed using the nominal values similar to those given in Hunt and Bowman (2004). The dose interval here and in the rest of the paper is $\Omega = [0, 0.15]$ for our application. We observe that all the locally D-optimal designs for different nominal values have 4 doses and require equal proportions of observations at the doses. All include the zero dose in the design.

The table also shows the D-efficiency of the design

$$\xi_u = \{0, 0.025, 0.05, 0.1, 0.15; 1/5, \ldots, 1/5\}$$

that closely approximates the one implemented in the developmental toxicity study of diethylhexl phthalate (DEHP) reported in Hunt and Bowman (2004). In what is to follow, we refer ξ_u as the implemented design for convenience. There was no rationale provided for the choice of ξ_u in their paper but we note that the design resembles a somewhat uniform design with equal weights over a set of log-uniformly spaced doses in Ω. Such designs may be intuitively appealing but it can be very inefficient, depending on the aims of the study. For example, row 1 in Table 1 lists the locally optimal design when the the nominal value is $\theta^{(0)} = (170, 0.04, 1.46, 40)$ and shows that its D-efficiency for estimating the threshold dose is only 34.6%. The D-efficiency of the ξ_u for estimating the model parameters is 80% so this design is 20% less efficient than the design ξ_0. As Table 1 shows the D-efficiencies of ξ_u can drop to 61% for other neighboring values of θ_0. Even when there is good rationale for a uniform design, the choice for the number of design points can also be problematic (Wong and Lachenbruch, 1996).

Because locally optimal design depends on nominal values of the parameters, it is instructive to study the problem of the mis-specification of the true values of parameters. To this end, we calculate the D-efficiency of the design $\xi_0 = \xi_D^*(\theta^{(0)})$ which is D-optimal for $\theta^{(0)} = (170, 0.04, 1.46, 40)$ and compute its efficiency for other values in the neighborhood of $\theta^(0)$. Table 1 shows the locally D-optimal design is relatively robust to small mis-specification of the nominal values displayed in the table. The biggest drop in D-efficiency occurs when τ was over-specified by 0.1 unit and the nominal values are given in the third row in Table 1. Even then the D-efficiency is still 70% for the range of nominal values shown in the table. Such sensitivity analysis is useful because in practice we do not know the true values of the model parameters and mis-specification in the nominal values can result in unacceptable loss in efficiency.

The locally optimal designs for estimating τ were determined from Lemma 2 in the appendix. Table 1 shows the D and τ-efficiencies of the design ξ_u. The τ-efficiencies are uniformly low, implying that the implemented design in the DEHP study does not estimate the threshold value well at all. The second and third last columns also show

Table 1: Locally D-optimal designs $\{d_0 = 0, d_1, d_2, d_3; 1/4, 1/4, 1/4, 1/4\}$ for the Hunt-Bowman model for different nominal values. The D-and τ-efficiencies of the design ξ_u are given, along with the D-efficiencies of $\xi_0 = \xi_D^*(\theta^{(0)})$ and $\theta_0 = (170, 0.04, 1.86, 40)^T$.

c_1	τ	β_0	β_1	d_1	d_2	d_3	$\text{eff}_D(\xi_u)$	$\text{eff}_D(\xi_0)$	$\text{eff}_\tau(\xi_u)$
170	0.04	1.46	40	0.020	0.04	0.0991	0.80	1	0.346
170	0.03	1.46	40	0.015	0.0404	0.0926	0.61	0.93	0.583
170	0.05	1.46	40	0.025	0.05	0.1090	0.86	0.70	0.405
170	0.04	1.26	40	0.020	0.0454	0.0976	0.81	0.98	0.420
170	0.04	1.66	40	0.020	0.04	0.1026	0.77	0.99	0.279
170	0.04	1.46	30	0.020	0.04	0.1188	0.75	0.94	0.205
170	0.04	1.46	50	0.020	0.0483	0.0901	0.76	0.88	0.541

the D-optimal designs are generally more robust to mis-specification of the nominal values than the implemented design.

Our numerical locally h-optimal designs have 3 dose levels and all have the form $\{0, \tau/2, \tau; w_0, 0.5, 0.5 - w_0\}$ for the nominal values displayed in Table 2. More design points are possible; for example, when $\theta^{(0)} = (170, 0.04, 1.86, 40)^T$, the locally h-optimal design is $\xi_h^*(\theta^{(0)}) = \{0, 0.020, 0.0479, 0.125; 0.3174, 0.5029, 0.1644, 0.0153\}$. For the same set of nominal values, we also observe that the implemented design ξ_u always has lower than 50% efficiencies for estimating the presence of hormesis and when $\theta = (170, 0.03, 1.46, 40)^T$, this efficiency is only 16.4%.

Table 2: Locally h-optimal designs $\{d_0 = 0, d_1, d_2; w_0, w_1, w_2\}$ for the Hunt-Bowman model and h-efficiencies of the design ξ_u for various nominal values.

c_1	τ	β_0	β_1	d_1	d_2	w_0	w_1	w_2	$\text{eff}_h(\xi_u)$
170	0.04	1.46	40	0.020	0.040	0.359	0.5	0.141	0.474
170	0.03	1.46	40	0.015	0.030	0.367	0.5	0.133	0.164
170	0.05	1.46	40	0.025	0.050	0.327	0.5	0.173	0.499
170	0.04	1.26	40	0.020	0.040	0.378	0.5	0.123	0.463
170	0.04	1.66	40	0.020	0.040	0.342	0.5	0.158	0.486
170	0.04	1.46	30	0.020	0.040	0.315	0.5	0.185	0.489
170	0.04	1.46	50	0.020	0.040	0.389	0.5	0.111	0.459

3.2 Criterion-robust Designs for the Hunt-Bowman Model

It is well known that optimal designs constructed under one criterion can perform poorly under another (Wong, 1994, Moerbeek, 2005). Consequently, it is always desirable to have a design that is robust under different criteria. This is especially so when there are explicit multi-objectives at the onset of the study. In this subsection, we first

construct a criterion-robust design that provides relatively high efficiency for our first two criteria: D- and τ-efficiencies. Formally, a criterion-robust design maximizes the minimum of D- and τ-efficiencies, that is

$$\min\{\text{eff}_D(\xi), \text{eff}_\tau(\xi)\} \to \max_\xi . \tag{2}$$

Generalization of this robust criterion to 3 or more objectives are possible; in our case, we may want to maximize the minimum of the efficiencies across all three criteria, i.e.

$$\min\{\text{eff}_D(\xi), \text{eff}_\tau(\xi), \text{eff}_h(\xi)\} \to \max_\xi . \tag{3}$$

We call (2) and (3) criterion (2) and criterion (3) respectively. Here and throughout, the following iterative algorithm is used to compute maximin or robust designs. First, we maximize the optimality criterion within the class of all s-point designs where the initial value of s we choose is the number of parameters in the model. The resulting design is a s-point maximin optimal design. Such designs are typically easier to find numerically than maximin optimal designs, which have no restriction on the number of design points in the optimization problem. For optimization, we employ the Nelder-Mead algorithm in the MATLAB package. After the optimal s-point maximin design is found, we consider the class of all $(s+1)$-point designs and find an optimal design within this class and repeat the procedure. At each iteration, we increase the number of points by one, until there is no change in the criterion value. Maximin optimal designs are found when further search within the class of designs with more points results in a design that has zero weight at some of the predetermined number of points.

Our numerical results show that the criterion-robust design for criterion (2) is $\{0, 0.020, 0.040, 0.098, 0.104; 0.381, 0.099, 0.419, 0.097, 0.004\}$ and its D and τ-efficiencies are both equal to 0.799. The criterion (3) involves D, h and τ-optimality and the criterion-robust design is $\{0, 0.021, 0.040, 0.098, 0.112; 0.389, 0.249, 0.329, 0.031, 0.001\}$. Its D, h and τ-efficiencies are all equal to 0.714, and both optimal designs have 5-points.

4 Alternative Models

There are two drawbacks of the Hunt-Bowman model. First, it has a derivative that is not continuous at the hormesis threshold dose level and second, its u-shape curve, by definition, has symmetry at low dose levels. The second restriction can be a serious limitation because non-symmetry may be an important feature in some applications; see, for example, Figure 4 in Calabrese and Baldwin (2003). When hormesis is not present in the single-agent/response scenario, the Hunt-Bowman model simplifies to the simpler Schwartz's threshold model (Schwartz, el at., 1995):

$$\mu(d) = \mu(d, \beta_0, \beta_1, \tau) = \begin{cases} \frac{1}{1+e^{\beta_0}} & 0 \le d \le \tau, \\ \frac{1}{1+e^{\beta_0 - \beta_1(d-\tau)}} & d \ge \tau. \end{cases} \tag{4}$$

Dette el at. (2008) considered a variety of models and constructed optimal designs for obtaining the best estimates for several characteristics in a dose-finding study. They showed that more flexible models can improve parameter estimateion. As alternatives, we propose smooth analytic models that do not possess a threshold dose level parameter explicitly. Specifically, we use a mean function that is a sum of an exponential decay curve and a sigmoidal curve. In particular, we propose two models: one has the form

$$\mu(d) = \mu(d, c_0, c_1, \beta_0, \beta_1) = c_0 e^{-c_1 d} + \frac{1}{1 + e^{\beta_0 - \beta_1 d}}, \tag{5}$$

which is a sum of an exponential decay model and a logistic model, and the other is

$$\mu(d) = \mu(d, c_0, c_1, \beta_0, \beta_1, \beta_2) = c_0 e^{-c_1 d} + \left(1 - \beta_0 e^{\beta_1 d^{\beta_2}}\right), \tag{6}$$

which is a sum of an exponential decay model and a Weibull model. The Weibull model was suggested by Chen and Kodell (1989) for describing dose-response relationship in toxicity studies. Other possible sigmoidal growth models that may be used are the Gomperts, Richards and Morgan-Mercer-Flodin models given respectively by

$$\beta_0 e^{-\beta_1 e^{-\beta_2 d}}, \quad \frac{\beta_0}{(1 + \beta_1 e^{-\beta_2 d})^{\beta_3}}, \quad \frac{\beta_1 + \beta_0 d^{\beta_3}}{\beta_2 + d^{\beta_3}}, \quad (\beta_0 = 1).$$

Still another model is the Chen-Kodell's model that assumes an increasing response

$$\mu(d) = \mu(d, \beta_0, \beta_1, \beta_2) = 1 - e^{\beta_0 - \beta_1 d^{\beta_2}}. \tag{7}$$

Several such dose-response relationships are displayed in Figure 1. We observe that models (5) and (6) are quite flexible for practical applications and do not have the drawbacks noted for the Hunt-Bowman model. The hormesis threshold for these models is an implicit parameter and the vector $b(\theta)$ required in the c-optimality design criterion can be directly obtained from the implicit function theorem and shown to be

$$b(\theta) = -\left.\frac{\partial \mu(d, \theta)}{\partial \theta} \Big/ \frac{\partial \mu(d, \theta)}{\partial d}\right|_{d=\tau(\theta)}.$$

The resulting c-optimal design minimizes the asymptotic variance of the estimated implicit threshold parameter in the model.

We fit some of the above models to the teratology data set digitized from Figure 1 in Hunt and Bowman (2004). For convenience, we refer to models given in (5) and (6) as the exp+log and the exp+weib models respectively. Figure 2 displays the dose-response curves for these models and the observed proportions for each dose group.

Table 3 shows the estimates for the expected response probability at each dose level for the exp+log, exp+weib, Hunt-Bowman, Chen-Kodell and Schwartz's models. We note that sum of squares of error (SSE) from the exp+log model is roughly the same as that from the Hunt-Bowman model, suggesting that smooth models can fit such data as well as threshold models. Other goodness of fit measures show similar results.

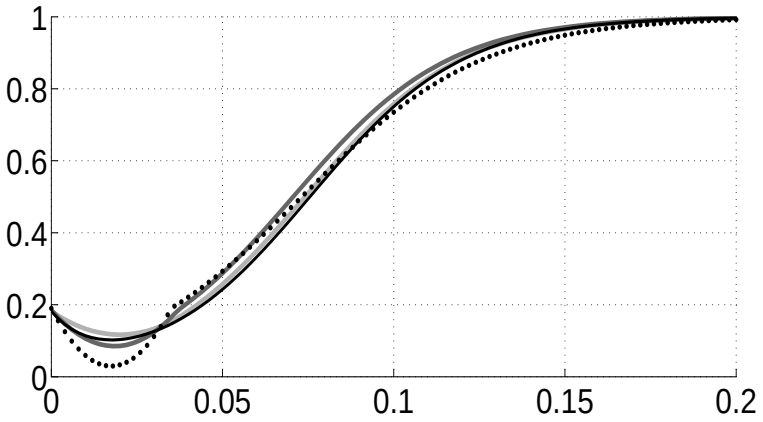

Figure 1: *Dose-response curves for the piecewise quadratic-logistic for different nominal values of* θ*:* $\theta = (834, 0.035, 1.45, 38)^T$ *(dotted),* $\theta = (164, 0.04, 1.5, 44)^T$ *(light gray),* $\theta = (294, 0.037, 1.48, 44)^T$ *(dark gray). The black solid line corresponds to the fitted response from the exp+logistic model when* $\theta = (0.15, 85, 3.4, 45)^T$*.*

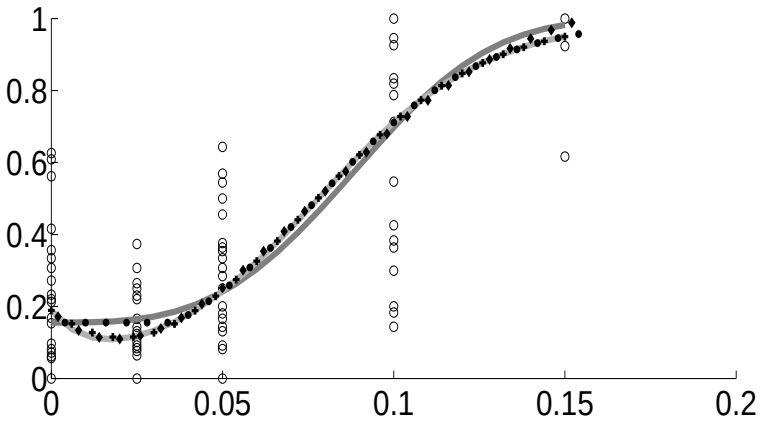

Figure 2: *The Hunt-Bowman, Schwartz, Chen-Kodell and the exp+log models have similar fits for their mean responses based on the teratology data.*

Table 3: Observed and fitted response probability $\mu(d_i)$ at the dose level d_i, $i = 0, 1, 2, 3, 4$ using various models.

dose	number of litters	exp+weib	exp+log	Hunt-Bowman	Chen-Kodell	Schwartz	observed proportions
		(6)	(5)	(1)	(7)	(4)	
$d_0 = 0.000$	30	0.1889	0.1889	0.1889	0.1554	0.1552	0.1889
$d_1 = 0.025$	26	0.1162	0.1181	0.1162	0.1647	0.1552	0.1162
$d_2 = 0.050$	26	0.2514	0.2423	0.2435	0.2407	0.2435	0.2514
$d_3 = 0.100$	24	0.6961	0.7114	0.7115	0.6974	0.7115	0.6961
$d_4 = 0.150$	25	0.9816	0.9504	0.9497	0.9823	0.9497	0.9816
SSE		4.6636	4.6958	4.6963	4.7614	4.7700	

4.1 Locally Optimal Designs for the Exponential+Logistic Model

The regression vector for the exp+log model is

$$f(d,\theta) = \left(e^{-c_1 d}, -c_0 d e^{-c_1 d}, -\frac{e^{\beta_0-\beta_1 d}}{(1+e^{\beta_0-\beta_1 d})^2}, \frac{d e^{\beta_0-\beta_1 d}}{(1+e^{\beta_0-\beta_1 d})^2} \right)^T.$$

Table 4 shows the locally D-optimal designs for the exp+log model and the relative efficiencies of the implemented design ξ_u in the DEHP study for various nominal values. The locally D-optimal design does not depend on the parameter c_0 because this parameter enters linearly in the mean response function. Numerical calculation shows that the locally D-optimal design has 4 points and always contains the zero dose. The table shows the D-efficiencies of the locally D-optimal design $\xi_0 = \xi_D^*(\theta)|_{\theta=(0.15,89,3.2,41)}$ when other nominal values are used. These D-efficiencies indicate how sensitive the design ξ_0 is to mis-specification of the nominal values. For the nominal values we looked at, all are at least 82% suggesting that ξ_0 is robust to mis-specification of the nominal values. The corresponding D-efficiencies for the design ξ_u range from 57% to 72%, suggesting that this design is more costly to use when nominal values are misspecified. The last two columns shows the estimated threshold τ and the maximum efficiency of the implemented design ξ_u for estimating τ is 36.5% for the nominal values considered.

Table 4: Locally D-optimal design $\{d_0 = 0, d_1, d_2, d_3; 1/4, 1/4, 1/4, 1/4\}$ for the exp+log model for different nominal values. The D-efficiencies of designs ξ_u and $\xi_0 = \xi_D^*(\theta)|_{\theta=(0.15,89,3.2,41)}$ and the estimated threshold τ are given at the penultimate last 3 columns. The last column shows the τ-efficiencies of the design ξ_u.

c_0	c_1	β_0	β_1	d_1	d_2	d_3	$\text{eff}_D(\xi_u)$	$\text{eff}_D(\xi_0)$	τ	$\text{eff}_\tau(\xi_u)$
0.15	89	3.2	41	0.0109	0.0558	0.1051	0.65	1	0.042	0.306
0.15	70	3.2	41	0.0134	0.0579	0.1063	0.72	0.99	0.041	0.333
0.15	110	3.2	41	0.0090	0.0543	0.1043	0.57	0.99	0.042	0.285
0.15	89	2.4	41	0.0103	0.0433	0.0893	0.60	0.92	0.028	0.274
0.15	89	4.0	41	0.0112	0.0727	0.1233	0.65	0.90	0.058	0.230
0.15	89	3.2	30	0.0112	0.0734	0.1422	0.72	0.82	0.058	0.281
0.15	89	3.2	50	0.0106	0.0472	0.0870	0.59	0.90	0.034	0.365

Hormesis is ascertained via the hypothesis testing framework after identifying the vector $h(\theta)$n in Section 2. This vector is complicated for the exp+log model and the exp+weib model and we do not display it. Table 5 shows selected locally h-optimal designs for the exp+log model and the h-efficiencies of ξ_0 and ξ_u. Again, for the nominal values we investigated, the table shows these efficiencies for the implemented design ξ_u are unacceptably low, ranging from 10.7% to 29.6%; in contrast, the locally D-optimal design has at least 83.9% for estimating the presence of hormesis in the study. Tables 4 and 5 show that the implemented design ξ_u estimates both the threshold dose and

the presence of hormesis poorly. The τ-efficiencies range from 23% to 36.5% and the h-efficiencies range from 10.5% to 29.6%. The locally τ-optimal design for the exp+log model is singular and takes all observations at τ, that is $\xi_\tau^*(\theta) = \{\tau(\theta); 1\}$.

Table 5: Locally h-optimal design $\{d_0 = 0, d_1, d_2, d_3; w_0, w_1, w_2, w_3\}$ for the exp+log model for different nominal values. The last two columns show that h-efficiencies of designs ξ_u and $\xi_0 = \xi_h^*(\theta)|_{\theta=(0.15,89,3.2,41)}$.

c_0	c_1	β_0	β_1	d_1	d_2	d_3	w_0	w_1	w_2	w_3	$\text{eff}_h(\xi_u)$	$\text{eff}_h(\xi_0)$
0.15	89	3.2	41	0.0108	0.0526	0.1187	0.371	0.501	0.087	0.041	0.193	1
0.15	70	3.2	41	0.0129	0.0564	0.1206	0.370	0.491	0.090	0.049	0.296	0.956
0.15	110	3.2	41	0.0091	0.0492	0.1174	0.372	0.508	0.085	0.035	0.107	0.954
0.15	89	2.4	41	0.0096	0.0430	0.1034	0.364	0.475	0.104	0.056	0.166	0.777
0.15	89	4.0	41	0.0118	0.0651	0.1362	0.377	0.528	0.066	0.029	0.216	0.943
0.15	89	3.2	30	0.0113	0.0648	0.1500	0.372	0.511	0.087	0.030	0.221	0.939
0.15	89	3.2	50	0.0103	0.0457	0.0986	0.370	0.493	0.089	0.048	0.186	0.839

4.2 Locally Optimal Designs for the Exponential+Weibull Model

The regression vector for the exp+weib model is

$$f(d,\theta) = \left(e^{-c_1 d}, -c_0 d e^{-c_1 d}, -e^{\beta_0 - \beta_1 d^{\beta_2}}, d^{\beta_2} e^{\beta_0 - \beta_1 d^{\beta_2}}, \beta_1 d^{\beta_2} \ln(d) e^{\beta_0 - \beta_1 d^{\beta_2}}\right)^T.$$

The locally D-optimal design for this model does not depend on parameters c_0 and β_0 because they appear linearly in the mean function. Consequently, we do not vary their nominal values in Table 6 that shows selected locally D-optimal designs and the D-efficiencies of the implemented design ξ_u. We observe that for the nominal values in the table, the locally D-optimal designs have 5 doses and always include the two extreme doses. The table shows locally D-optimal designs have at least 82% efficiencies for estimating the model parameters compared with at least 72% D-efficiencies for the implemented design ξ_u. Further, efficiency of ξ_u for estimating τ can be as low as 2.9%, suggesting that the implemented design ξ_u is a poor design to use for the study.

Table 7 shows the locally h-optimal designs for the exp+weib model. These design have larger weights at the low dose levels and appear to be sensitive to the parameter β_2 and not sensitive to other parameters. Again it is clear from the table that locally D-optimal designs outperform the implemented design ξ_u by a wide margin in terms of assessing the presence of hormesis. Additional results not shown here also show τ-efficiencies of the design ξ_u for estimating the threshold are generally low and average about 40%. These 2 tables show ξ_u estimate τ and the presence of hormesis quite poorly. As in the exp+log model, our results show that the locally τ-optimal design for the exp+weib model requires that we take all observations at τ, that is $\xi_\tau^*(\theta) = \{\tau(\theta); 1\}$.

Table 6: Locally D-optimal designs $\{d_0 = 0, d_1, d_2, d_3, d_4 = 0.15; 1/5, \ldots, 1/5\}$ for the exp+weib model for different nominal values. The D-efficiencies of designs ξ_u and $\xi_0 = \xi_D^*(\theta)|_{\theta=(0.9,10.5,0.55,65,1.8)}$ and the estimated τ are given in the last 3 penultimate columns. The last column shows the D-efficiencies of the design ξ_u for estimating τ.

c_0	c_1	β_0	β_1	β_2	d_1	d_2	d_3	$\text{eff}_D(\xi_u)$	$\text{eff}_D(\xi_0)$	τ	$\text{eff}_\tau(\xi_u)$
0.9	10.5	0.55	65	1.8	0.0161	0.0535	0.1047	0.92	1	0.040	0.297
0.9	7.5	0.55	65	1.8	0.0160	0.0537	0.1050	0.92	0.99	0.028	0.244
0.9	13.5	0.55	65	1.8	0.0159	0.0532	0.1042	0.92	0.99	0.050	0.202
0.9	10.5	0.55	45	1.8	0.0167	0.0565	0.1092	0.91	0.99	0.059	0.166
0.9	10.5	0.55	85	1.8	0.0151	0.0509	0.0998	0.92	0.99	0.029	0.270
0.9	10.5	0.55	65	1.5	0.0091	0.0361	0.0827	0.72	0.82	0.007	0.029
0.9	10.5	0.55	65	2.1	0.0222	0.0665	0.1167	0.87	0.94	0.085	0.191

Table 7: Locally h-optimal design $\{d_0 = 0, d_1, d_2, d_3, d_4 = 0.15; w_0, w_1, w_2, w_3, w_4\}$ for the exp+weib model for different nominal values of the parameters. The h-efficiencies of designs ξ_u and $\xi_0 = \xi_D^*(\theta)|_{\theta=(0.9,10.5,0.55,65,1.8)}$ are shown in the last 2 columns.

c_0	c_1	β_0	β_1	β_2	d_1	d_2	d_3	w_0	w_1	w_2	w_3	w_4	$\text{eff}_h(\xi_u)$	$\text{eff}_h(\xi_0)$
0.9	10.5	0.55	65	1.8	0.0129	0.0534	0.1105	0.299	0.389	0.146	0.109	0.056	0.424	1.000
0.9	7.5	0.55	65	1.8	0.0129	0.0535	0.1108	0.303	0.393	0.145	0.106	0.052	0.419	0.999
0.9	13.5	0.55	65	1.8	0.0127	0.0531	0.1101	0.296	0.382	0.145	0.114	0.063	0.431	0.997
0.9	10.5	0.55	45	1.8	0.0133	0.0565	0.1150	0.296	0.386	0.147	0.113	0.058	0.403	0.984
0.9	10.5	0.55	85	1.8	0.0121	0.0499	0.1054	0.302	0.391	0.143	0.107	0.057	0.431	0.968
0.9	10.5	0.55	65	1.5	0.0071	0.0354	0.0859	0.290	0.386	0.157	0.108	0.058	0.148	0.218
0.9	10.5	0.55	65	2.1	0.0185	0.0667	0.1214	0.319	0.404	0.137	0.096	0.044	0.398	0.726

5 Robust Designs

In this section we construct criterion-robust and model-robust designs that offer some protection when we change the design criterion and model assumptions. We first present designs that are robust to two and three optimality criteria for the exp+log model and the exp+weib model before we construct designs that are robust to model assumptions. All of these designs have to be determined numerically.

We recall that Criterion (2) concerns estimating all model parameters and the threshold parameter. Criterion (3) additionally estimates the existence of hormesis. For the exp+log model with $\theta = (0.15, 89, 3.2, 41)^T$, the criterion robust design for criterion (2) is $\{0, 0.13, 0.049, 0.109; 0.106, 0.137, 0.632, 0.125\}$. Both the D and τ-efficiencies are 71%. For criterion (3), $\{0, 0.13, 0.048, 0.117; 0.172, 0.272, 0.510, 0.046\}$ is the corresponding criterion robust design. Its D-efficiency is 66.8% and both its τ and h-efficiencies are 57.8%.

For the exp+weib model with $\theta = (0.9, 10.5, 0.55, 65, 1.8)^T$, the criterion robust design for criterion (2) is $\{0, 0.19, 0.043, 0.105, 0.150; 0.089, 0.129, 0.604, 0.091, 0.088\}$

and both its D and τ-efficiencies are 65.7%. The corresponding criterion robust design for criterion (3) is $\{0, 0.018, 0.044, 0.108, 0.150; 0.134, 0.244, 0.532, 0.061, 0.029\}$. Its D-efficiency is 60% and both its τ and h-efficiencies are 59.3%. For the cases considered here, the criterion-robust designs for the exp+log model has 4 points and the criterion-robust designs for the exp+weibull model has 5 points, regardless of the number of criteria involved. As expected, efficiencies always drop when an additional criterion is introduced because of more stringent demands on the design.

In developmental studies, there are several plausible dose-response models for describing the binary outcomes. Consequently, it is desirable to design the study so that we have efficient estimates no matter which one of a few plausible models holds. For this purpose, we construct robust designs that maximizes the minimal D- and τ-efficiency for models for a few competing models and the maximization is either over a set of designs with a pre-determined of points or over the set of all continuous designs. The resulting design will ensure that we have the best possible efficiency for estimating model parameters and the presence of hormesis as long as the true model is correctly identified as one of the plausible models. Specifically, we want to find a design that has the following property:

$$R(\xi|I) := \min_{i \in I} \min\{\text{eff}_D^{(i)}(\xi), \text{eff}_\tau^{(i)}(\xi)\} \to \max_\xi$$

where I is a set of models. We are primarily concerned with two choices of I: I_2 is the set consisting 2 plausible models: the Hunt-Bowman and exp+log models and I_3 is the set consisting 3 plausible models: the Hunt-Bowman, exp+log and exp+weib models.

In what is to follow, the following nominal values for the parameters in these models are assumed: $\theta = (170, 0.04, 1.46, 40)^T$ for the Hunt-Bowman model, $\theta = (0.15, 89, 3.2, 41)^T$ for the exp+log model, $\theta = (0.9, 10.5, 0.55, 65, 1.8)^T$ for the exp+Weib model. Again, all the maximin robust designs are found numerically and they depend on the set where the maximization is taken. For example, we found that the robust design that maximizes $R(\xi|I_3)$ among all 5-point designs is the design that takes observations at dose levels $0, 0.024, 0.045, 0.107$ and 0.150 with weights given by $0.268, 0.174, 0.477, 0.055$ and 0.026. The minimal efficiency of this design is 56.6%. If we maximize the set of all designs with 6 points, the maximin optimal design now takes observations at dose levels $0, 0.016, 0.040, 0.044, 0.103$ and 0.150 with weights given by $0.230, 0.084, 0.247, 0.337, 0.060$ and 0.041. The minimal efficiency of this design is 59.6%. If we further enlarge this set to all designs with 7 or more points, the resulting maximin robust design will not provide a larger minimal efficiency and we conclude that this is also the maximin robust design. The corresponding maximin robust design for the case when we wish to maximize $R(\xi|I_2)$ requires doses at $0, 0.015, 0.046$ and 0.108 with weights given by $0.288, 0.072, 0.572$ and 0.068. The minimal efficiency of this design is 62.5%. Not surprisingly, this efficiency is higher than the two previous efficiencies because there are fewer competing models under consideration.

6 Conclusions

In this work, we discussed design issues for assessing hormetic effects and provided optimal designs for estimating threshold value, model parameters and whether hormesis exists. We proposed smooth models that are competitive with models that have an explicit threshold and found designs that are robust under a variation of design criteria and model assumptions. When we compared our designs with a design similar to the one implemented in a study reported by Hunt and Bowman (2004), our designs have uniformly higher efficiencies for attaining the experimental goals. Our proposed designs therefore can rein in cost, reduce the number of animals used in the study and at the same time provide more accurate statistical inference.

Unlike the Hunt-Bowman model, some of our proposed optimal designs also enjoy invariant properties that allow us to deduce how the locally optimal design changes when the dose interval is changed in a meaningful way. For example consider the exp+log model with parameter $\theta = (c_0, c_1, \beta_0, \beta_1)^T$ on the dose interval $[0, T]$ and we wish to determine how the optimal designs change when we expand the dose interval from $[0, T]$ to $[0, \gamma T]$ and γ is a user-selected positive number. To this end, let $t_i^*(c_0, c_1, \beta_0, \beta_1, T)$ be the ith design point of the D-, τ- or h-optimal design on $[0, T]$ with corresponding weight $w_i^*(c_0, c_1, \beta_0, \beta_1, T)$. It can be shown that the optimal design on the interval $[0, \gamma T]$ has the following design points and weights:

$$\gamma t_i^*(c_0, c_1, \beta_0, \beta_1, T) = t_i^*(c_0, c_1/\gamma, \beta_0, \beta_1/\gamma, \gamma T),$$

$$w_i^*(c_0, c_1, \beta_0, \beta_1, T) = w_i^*(c_0, c_1/\gamma, \beta_0, \beta_1/\gamma, \gamma T).$$

The corresponding results for the exp+weib model when the dose interval is changed from $[0, T]$ to $[0, \gamma T]$ are

$$\gamma t_i^*(c_0, c_1, \beta_0, \beta_1, \beta_2, T) = t_i^*(c_0, c_1/\gamma, \beta_0, \beta_1/\gamma^{\beta_2}, \beta_2, \gamma T),$$

$$w_i^*(c_0, c_1, \beta_0, \beta_1, \beta_2, T) = w_i^*(c_0, c_1/\gamma, \beta_0, \beta_1/\gamma^{\beta_2}, \beta_2, \gamma T).$$

We close with a note that a common critique of optimal designs is that they have too few points to be useful in practice. For example, some of our optimal designs do not have enough points to detect lack of fit in the model. We remind readers that one of the main uses of optimal designs is to calibrate the worth of any design. If the researcher likes to have more design points and change the weights at some points, the researcher can use the optimal design as a guide how to adjust the design. Absent this guidance, practitioners tend to frequently use designs without good rationale resulting in waste of resources, as we demonstrated here with the use of the implemented design ξ_u reported in Hunt and Bowman (2004). In general, the selected design should be selected carefully and not stray too far away from the optimum where its efficiencies become unacceptable.

Acknowledgements. All authors were partially supported by a NIH grant award R01GM072876. The work of Wong was also partially by NIH grant award P01CA109091.

The work of Dette has been supported in part by the Collaborative Research Center "Statistical modeling of nonlinear dynamic processes" (SFB 823) of the German Research Foundation (DFG).

7 Appendix

The following technical result is helpful for our present work. It is a reformulation of the equivalence theorem for c-optimality given in Pukelsheim (1993).

Lemma 1. *If $f_1(d), \ldots, f_m(d)$ are linearly independent continuous functions on the interval $[0, \bar{d}]$, the design ξ is c-optimal if and only if there exists a vector $q \in \mathbb{R}^m$, such that the generalized polynomial $q^T f(d)$ satisfies the following conditions for some $\nu > 0$:*

(i) $q^T f(d_i) = (-1)^i \qquad i = 1, \ldots, m$

(ii) $|q^T f(d)| \leq 1 \qquad$ *for all* $\quad d \in [0, \bar{d}]$

(iii) $Fw = \nu c,$

where $F = ((-1)^j f_i(d_j))_{i,j=1}^{m,k}$ and $w = (w_1, \ldots, w_k)$. Moreover, $c^T M^-(\xi) c = 1/\nu^2$.

The next lemma describes locally optimal designs for the Hunt-Bowman model.

Lemma 2: *For the Hunt-Bowman model defined on the dose interval $[0, \bar{d}]$,*

(i) *the locally τ-optimal design is singular and has design points points at 0 and τ, that is $\xi_\tau^*(\theta) = \{0, \tau(\theta); 1/2, 1/2\}$;*

(ii) *the locally D-optimal design does not depend on the parameter c_1 and it has at most 3 design points on $[0, \tau]$ and at most 2 points on $[\tau, \bar{d}]$.*

(iii) *the locally h-optimal design has at least 3 design points.*

Proof. Since τ is a component of the vector θ, we have $b(\theta) = (0, 1, 0, 0)^T$. Part (iii) of Lemma 2 holds because $\nu b(\theta) = f(0, \theta)/2 - f(\tau, \theta)/2$ and $\nu = c_1 \tau$. If we let $q = (0, -2/(\tau c_1), \frac{(1+e^{\beta_0})^2}{e^{\beta_0}}, q_4)$, we have $q^T f(d) = 2d/\tau - 1$ on the interval $[0, \tau]$. Note that q_4 can be chosen to ensure the inequality $\max |q^T f(d)| < 1$ holds on $[\tau, \bar{d}]$. Consequently, parts (i) and (ii) of Lemma 1 hold. This justifies case (i) of the proposition.

To prove case (ii) of Lemma 2, we note that the locally D-optimal design does not depend on parameter c_1 because the D-optimality criterion has the form $c_1^{-2} \det M(\xi, \theta)$. Further, we note that the function $f^T(d) M^{-1}(\xi) f(d)$ is a linear combination of monomials $1, d, d^2, d^3, d^4$ on the interval $[0, \tau]$. Consequently, this function can have at most 3 local maxima. By the equivalence theorem (Kiefer, Wolfowitz, 1960) it follows that the locally D-optimal design has at most 3 design points on $[0, \tau]$. Similarly, the locally D-optimal design can have at most 2 design points on $[\tau, \bar{d}]$ because the function $f^T(d) M^{-1}(\xi) f(d)$ has at most 2 local maxima on the interval $[\tau, \bar{d}]$.

To prove the case (iii) of Lemma 2, we obtain directly that $h(\theta) = (-\tau, -c_1, 0, 0)^T$. By inspection, part (iii) of Lemma 1 cannot hold for any 1 or 2-point designs and so the locally h-optimal design has at least 3 design points.

□

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