Published in final edited form as:

Comput Methods Programs Biomed. 2013 September ; 111(3): 701–710. doi:10.1016/j.cmpb.2013.05.004.

Web-based tools for finding optimal designs in biomedical studies

Weng Kee Wong

Fielding School of Public Health, Department of Biostatistics, University of California at Los Angeles, 10833 Le Conte Ave, Los Angeles, CA 90095, USA. Telephone: 310 206 9622

Weng Kee Wong: wkwong@ucla.edu

Abstract

Experimental costs are rising and applications of optimal design ideas are increasingly applied in many disciplines. However, the theory for constructing optimal designs can be esoteric and its implementation can be difficult.

To help practitioners have easier access to optimal designs and better appreciate design issues, we present a web site at <http://optimal-design.biostat.ucla.edu/optimal/> capable of generating different types of tailor-made optimal designs for popular models in the biological sciences. This site also evaluates various efficiencies of a user-specified design and so enables practitioners to appreciate robustness properties of the design before implementation.

Keywords

continuous design; dose response design; multiple-objective optimal design

1 Introduction

Optimal experimental design theory and applications have been gaining in importance about two decades ago (Atkinson, 1996). A main reason is the rising cost in experimentation at all levels and researchers are looking for ways to design more efficient studies without sacrificing precision in statistical inference. Applications of optimal design ideas are increasingly applied to traditional disciplines in new and interesting ways and also to cross-disciplinary areas. In Berger and Wong (2005), they documented some recent applications of optimal design ideas to solve real problems, including developing optimal designs for groundwater modeling problems (McPhee and Yeh, 2005) and designing an optimal design in the measurement of cerebral blood flow using the Kety-Schmidt technique (Matthews and James, 2005). Optimal designs have also been developed for longitudinal studies, see for example, Ouwens-Mario et al. (2002) and Tekle et al. (2008).

One of the main beneficiaries of optimal design theory and applications is the pharmaceutical industry. Drug development is very time consuming and typically requires

© 2013 Elsevier Ireland Ltd. All rights reserved.

Conflict of Interest

None

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

the agent to go through different phases of research. In Phase I and Phase II trials, design strategies explore and target inference on various parameters of the agent characteristics using a dose response model. There is a huge literature on dose finding and optimal designs for Phase I and Phase II trials, see for example, Rosenberger and Haines (2002) and the references therein where they reviewed competing designs and techniques for early Phase I trials. Because model assumptions are required to study drug characteristics, dose response and dose finding designs invariably require a heavy dose of optimal design theory to come up with practical design strategies, see for example, Bretz, et al. (2010), Dette and Bretz (2010) and Bornkamp, et al. (2011). Increasingly, biomedical researchers are interested to find optimal designs for models with random effects, particularly pharmacometricians who seem to have a head start, beginning with Mentre et al. (1997) and continuing to date, see for example Ogungbenro et al. (2005) and, Mentre and Escolano (2006).

A quick online search reveals that there are many web sites that calculate sample size requirements for various types of statistical problems after the user supplies design parameters and assumptions for the problem. They vary greatly in sophistication and scope; many are free and some are commercially produced. Two examples are <http://www.stat.ubc.ca/rollin/stats/ssize/> and <http://homepage.stat.uiowa.edu/rleth/Power/>. Interestingly, despite the usefulness of optimal experimental designs, there is virtually no web site for finding different types of optimal experimental designs for a broad range of models. The aim of this paper is to present a new web site that generate different types of tailor-made optimal designs for a wide range of models. Here tailor-made means the user selects the design criterion, the statistical model and the parameters for the design problem that typically includes specifying the design space and nominal values for the model parameters if the mean function is nonlinear.

The next section briefly discusses background for continuous designs which is the focus here. Section 3 calls for a good web site for researchers in optimal design to collectively promote research and facilitate use of optimal design ideas for practitioners. Section 4 discusses our new web site, its features, advantages and limitations, along with a few demonstrations. Section 5 contains a summary and Section 6 acknowledges key collaborators in the creation of the site as well as reviewers of the web site.

2 Background

We focus on continuous designs first proposed by Kiefer in late 1950's. The approach was controversial initially but it appears now that the method is quite standard and used widely for determining optimal designs for nonlinear models. Kiefer (1985) is a voluminous documentation of his work in this area. Interestingly, design monographs almost all focus on continuous designs. Examples include Chernoff (1972), Fedorov (1972), Silvey (1980), Pazman (1986), Pukelsheim (1993), Schwabe (1996), Fedorov and Hackl (1997) and Flournoy et al. (1998). These monographs are technical with the exception of two introductory texts on optimal experimental designs by Atkinson et al. (2007), and, Berger and Wong (2009). Review papers on optimal experimental designs include Hill (1978), Aigner (1979), Atkinson (1998), Ford et al. (1989) and Wong (1999).

A continuous design is a probability measure defined on the given compact design space. The set up assumes a fully parametric model and the total sample size n is relatively large and fixed in advance. In practice, n is predetermined usually by the budget available for the experiment. The theory for continuous optimal design tells the researcher how many points (k) are required, where they are (x_i 's) and what proportions (p_i 's) of observations to take at these points. Clearly, the number of design points, where they are and what proportions of observations to take at these points depend on the optimality criterion and the statistical

model. It is well known that different optimality criteria can result in very different designs and this implies that an optimal design under one criterion can perform poorly under another. In practice, the number of observations at the point x_i is np_i^* after rounding each np_i to the nearest integer np_i^* , $i = 1, \dots, k$ and subject to the constraint $np_1^* + np_2^* + \dots + np_k^* = n$. In contrast, an optimal exact design requires us to determine for fixed n , a statistical model and a design criterion, the optimal values of k , $x_1, \dots, x_k$ and the number of observations $n_1, \dots, n_k$, to be taken at $x_1, \dots, x_k$, respectively, subject to $n_1 + \dots + n_k = n$. Finding an exact optimal design is considerably more difficult than finding a continuous optimal design because derivation of an exact optimal design usually requires involved mathematics and number theory.

A main advantage of the continuous design approach is that it is a practical and general way to construct continuous optimal designs for a statistical model. It is practical because the optimal design has the same structure for all values of n , unlike an exact optimal design whose structure may vary for different values of n , thereby requiring endless tables of exact optimal designs for each model, each criterion and each value of n . Following convention, the design criterion is some function of the Fisher information matrix, defined by the negative of the expectation of the second derivatives of the loglikelihood function with respect to the model parameters. For continuous designs, the design criterion is always a convex function so that convex analysis results can be used to determine whether a design is optimal among all designs on the given design space. A principal tool for checking design optimality is the equivalence theorem, which can also be used to provide a lower bound for the efficiency of the design if the design is not optimal and the optimal design is still unknown. When the design space is one or two dimensional and the criterion is differentiable, a graphical plot based on the equivalence theorem is usually used to check the optimality of a design. Such a plot is variously called a sensitivity plot, a directional derivative plot or more informally, an equivalence plot. When the design is optimal among all designs on the design space, the plot should be bounded above by a constant, typically zero, across the design space with equality at the optimal design points. On the other hand, if the design is not optimal, the plot will not be bounded above by a constant and equality will not be attained at all the design points. This implies that by looking at the plot, one can definitively conclude whether the design is optimal or not among all designs on the design interval. This is not true for optimal exact design, where there is no general tool for verifying optimality. Specific technical conditions will have to be derived and checked on a case by case basis to confirm optimality and in most cases, they are either not available or too difficult to verify when they are available.

Another advantage of working with continuous designs is that when an optimal design cannot be found analytically, a simple algorithm can usually be written to find the optimal design sequentially. In particular, if the criterion is differentiable and convex, there are algorithms that will converge to the optimal design. The iterative procedure typically starts with a user-selected design with a non-singular information matrix. Then a carefully selected point from the design space is added to the current design using a suitable weight to produce a new design. The above steps are repeated until convergence up to a user-selected tolerance level or termination when the stopping criterion is met. The latter can take the form on the maximum number of iterations allowed or when the successive criterion values do not change by an amount specified by the tolerance level. Details and variants of such algorithms are discussed in design monographs mentioned above. For non-differentiable optimality criteria such as min-max or max-min type of criteria, there is no algorithm that is guaranteed to converge to the optimal design.

Some common algorithms that come to mind for finding optimal experimental designs are Dykstra's method (Dykstra, 1971), DETMAX (Mitchell, 1974) and modified Fedorov

method (1972) all discussed in Cook and Nachtsheim (1980). Statistical software packages like SAS and JMP provide codes for generating some optimal designs for popular models, notably D -optimal designs for polynomial models in one or more factors. Almost all pertain to finding exact optimal designs, and not continuous designs which is the focus here. Some authors prefer to have their self-written codes on their home pages or email the codes to readers upon request. There are also some who seem to prefer to keep the codes to themselves for various reasons and not have them publicly available to promote their work. Perhaps one reason for not having their codes available is that they recognize it takes much more labor to have the codes "good enough" for public consumption. However there are good journals now that check and publish codes and give due credit for the effort and time for creating the software for statistical research. Hopefully such journals may help change the trend and bring about more quality and useful algorithms, not only for the design community, but for the statistical community at large.

3 Web-Based Tools for Generating Optimal Experimental Designs

Many publications in the biomedical literature use designs without any justification at all, or if they did, they did not report them. These designs may be practical or traditional but sometimes they do not perform well from the statistical viewpoint. Researchers should always give considerable attention to their choice of the design and include some justification. To promote greater use of optimal design ideas in practice, it is helpful to have a web site that generates optimal designs easily and compare designs. With easier access to optimal designs, practitioners may be more encouraged to incorporate optimal design ideas in their work to save cost without loss in the precision of the statistical inference. This may well lead to a reconsideration of the automatic use of their favorite or traditional designs,

There are other compelling motivations for a design web site that has the ability to generate various types of optimal designs. Statistical models are getting more complex as researchers seek to model their study more realistically. This means that optimal designs will have to be found numerically and algorithms will have to be implemented for practitioners. Further, formulae or analytical descriptions for some optimal design may be available in non-traditional journals and are scattered across a wide range of disciplines; a web site can serve to consolidate results for research purposes. Lastly, a design web site can inform practitioners of the importance of design and educate them on design options. For example, optimal design can be sensitive to model assumptions and a web-based tool can evaluate its robustness properties easily either with respect to another model or when additional points are added to the optimal design. Additionally, the site provides a useful resource for design researchers. For example, the A-optimal design for estimating the two parameters in the logistic model can be time consuming to determine but the answer is likely already available in the literature. A few keystrokes at the web site will produce the A-optimal design and save time for the researchers.

It is instructive to consider the following two simple examples to further illustrate the above issues. Example 1 shows that the formula for an optimal design can be complicated even for a simple model and the elegantly derived formula for the optimal design alone may be of limited use to practitioners. Example 2 illustrates several design questions are typically relevant for a seemingly straightforward design problem, suggesting a tailor-made multiple-objective design is more appropriate to capture the various aims in the study. The upshot is that an interactive web-based design tool will be helpful for practitioners to find an appropriate design for their problem and facilitate researchers study properties of optimal design.

3.1 Example 1

This example is taken from a doctoral thesis from the University of Glasgow and reported in Silvey (1980). Ford (1976) considered the two-parameter logistic model on the prototype design interval $X = [-1, 1]$ and wanted to find a locally D -optimal design for estimating the two parameters. Let $\pi(x)$ be the probability of a response at the dose level x and let the model be

$$\log \frac{\pi(x)}{1-\pi(x)} = \theta_1 + \theta_2 x,$$

where the vector of parameters $T = (\theta_1, \theta_2)$ has $\theta_1 > 0$ and $\theta_2 > 0$. Being a nonlinear model, the information matrix depends on the nominal values of the two parameters and consequently optimal designs are termed locally optimal designs (Chernoff, 1972).

Assuming the number of independent observations allowed for the study is pre-determined either by cost or time, the locally D -optimal design is always to take roughly equal number of observations from two doses. The two doses may or may not include the two extreme doses, depending on the nominal values of the two parameters. This result and its proof were given in Ford (1976) where he first defined two auxiliary quantities a and u^* : let a solve $\exp(z) = (z+1)/(z-1)$, i.e. $a = 1.54$ and let u^* solve $\exp(\theta_1 + \theta_2 u) = (2 + (u+1)\theta_2)/(-2 + (u+1)\theta_2)$. Ford (1976) showed that the locally D -optimal design is:

condition	locally D -optimal design
$\{\theta: \theta_2 - \theta_1 \geq a\}$	$\{\frac{a-\theta_1}{\theta_2}, \frac{-a-\theta_1}{\theta_2}; \frac{1}{2}, \frac{1}{2}\}$
$\{\theta: \theta_2 - \theta_1 < a, \exp(\theta_1 + \theta_2) \leq \frac{\theta_2+1}{\theta_2-1}\}$	$\{-1, u^*; \frac{1}{2}, \frac{1}{2}\}$
$\{\theta: \exp(\theta_1 + \theta_2) > \frac{\theta_2+1}{\theta_2-1}\}$	$\{-1, 1; \frac{1}{2}, \frac{1}{2}\}$

The locally D -optimal design depends on the nominal values of the parameters θ_1 and θ_2 and is given in the parentheses on the right hand side. The first two quantities denote the optimal dose levels which may depend on the unknown parameters θ_1 and θ_2 and the last two quantities denote the weights at the two doses. For this problem, the optimal weights are always equal. For example, if $\theta_2 = 2$ and $\theta_1 = 1$, the locally D -optimal design is equally supported at -1 and 0.3980 and, if $\theta_2 = 3$ and $\theta_1 = 1$, the locally D -optimal design is equally supported at -1 and 0.3978 . In terms of a dose response study, the results tell us to allocate equal number of patients at two doses and these two doses should correspond to the transformed values -1 and 0.3978 in the prototype interval. Data from such a design will guarantee that the estimates of the two parameters in the logistic model are the most accurate by ensuring that the area of the joint confidence region for the two parameters is the smallest among all designs defined on the scaled dose interval.

The formula for the design is indeed quite complicated for a relatively simple model and it is arrived at after tedious algebra. In some cases, sophisticated mathematics will have to be employed to find the optimal designs analytically. Because D -optimal designs are usually the simplest to derive, one can expect formulae will be more complicated for other types of optimal designs for the two-parameter logistic model.

While the above formula in Example 1 for the logistic model is remarkable, it is likely to fall short of the practitioner's expectations. It is instructive to ask the following design questions:

- what is the corresponding D -optimal design if the design interval is $[-2, 2]$ or $[1, 3]$?

- if only one of the two parameters is of interest, what is the optimal design for estimating the single parameter?
- if the parameter θ_2 is more interesting than the parameter θ_1 , what is the best design that would ensure the estimate for θ_2 is more precise than the estimate for θ_1 ?
- if a design with 3 or more points is desired, where should the additional point or points be?
- how is the performance of the 4-point uniform design compared with the locally D-optimal design?

3.2 Example 2

Consider the homoscedastic quadratic model defined on a given design interval, say, $X = [0, 3]$ given by

$$E(y) = \theta_0 + \theta_1 x + \theta_2 x^2.$$

Assuming errors are independent and identically distributed with mean 0 and a constant variance, a common design question is how to spread out a fixed number of observations for estimating θ_0 , θ_1 and θ_2 as accurately as possible. Like in Example 1, a D-optimal design is appropriate for this purpose because such an optimal design minimizes the confidence ellipsoid for all the three parameters. This is achieved by minimizing the determinant of the covariance matrix which is equivalent to maximizing the determinant of the Fisher information matrix. It is well known that the D-optimal design is equally supported at 0, 1.5 and 3.

Other design questions that may arise here may include (i) estimating θ_2 only, (ii) extrapolating at a given point, say $z = 4$ outside the design interval X or (iii) estimating the turning point of the quadratic given by

$$g(\theta) = -\frac{\theta_1}{2\theta_2}$$

when $\theta_2 \neq 0$. This location of the turning point is obtained by directly differentiating the mean function $E(y)$ with respect to x and solving the resulting equation for x . These three objectives seek to minimize the variance of a function of the estimated model parameters and so in each case, a c -optimal design is appropriate.

A more interesting design question is how to design to accurately estimate the response surface over a given dose range Z , for example $Z = [3, 5]$. This situation arises when it is only roughly known at the design stage that there is interest to extrapolate beyond $z = 3$ and it is not possible to specify precisely how far beyond the dose level $z = 3$. In dose response studies, drug concentrations outside the safety limits cannot be used but one can model and study average responses over a range of doses outside the safety limits. In such a situation, one may consider minimizing the largest variance among all variances of the estimated responses from the interval Z . This is a minimax type of criterion which is notoriously difficult to work with technically because the criterion now is not differentiable. Wong (1992), Wong and Cook (1993), King and Wong (1998) and Chen et al. (2011) constructed minimax optimal designs for linear models and, Dette and Wong (1999), and, King and Wong (2000) constructed minimax optimal designs for nonlinear models.

Some of the answers to questions posed in Example 1 may already be available in the literature and if so, they can be made available on a web site. This is part of the long term goal of our web site, where we also plan to provide quick answers to common and anticipated design questions from practitioners and also from statisticians who do not want to take time to search for an appropriate design from the literature.

In summary, the motivating factors for a web site to generate different types of optimal designs for various models are both compelling and plentiful, and worth repeating with the hope that our site will spur interest among design researchers to set up web-based tools to further promote use of optimal designs in practice. The reasons are (i) the mathematical theory and derivation of the optimal design are usually complicated and frequently, they may not be directly applicable for the particular setting the practitioner has; having a web site provides flexibility, (ii) some optimal designs are very tedious to compute even when it has an analytical description. For example, some optimal designs are characterized by canonical moments and so additional effort is required to determine the optimal designs (Dette and Studden (1997)); having a web site will mean that the computation is done automatically, (iii) optimal designs can be sensitive to model assumptions and having a design web site facilitates study of robustness properties of the optimal design, (iv) even for the theoretical researchers in the field, the availability of the optimal design after a few key strokes, along with a resource base that consolidates results in the field, can lead to useful conjectures of optimal designs for complicated models and their properties.

4 Web Sites for Finding Optimal Designs

The importance and usefulness of having a web site that enables researchers to generate optimal designs quickly have been recognized by pharmacometricians comprised largely of researchers in pharmacokinetics (PK) and pharmacodynamics (PD). This field seems to have taken a unique lead in terms of putting together web sites to generate optimal designs for their models and perform analyses. There are at least four groups from different countries that have established web sites for finding optimal designs. Dr. Mentre, et al. from the University of Paris Diderot in France have PFIM with codes written in R and the web site is at <http://www.pfim.biostat.fr/>. Another program is PopDes written in Matlab by Dr. Ogungbenro from the University of Manchester. The site address is <http://www.pharmacy.manchester.ac.uk/capkr/popdes/>. Professors Nyberg, Ueckert and Hooker from University of Uppsala in Sweden also have a program called PopED written in Matlab and housed at <http://poped.sourceforge.net/>. Still another program called WinPOPT/POPT is also available at <http://www.winpopt.com/>. The codes are in Matlab and its owner is Professor S. Duffull from the University of Otago in New Zealand. These web sites all have a common focus on PK/PD models with similar capabilities and many results from these separately developed web sites have been compared and validated. There are still some that do not explicitly have a web site but their codes are available upon request. One example is the program PKstamp written in MATLAB code from Drs. Sergei Leonov and Aliev.

Recently, we establish a web site that generates a variety of optimal designs for different models commonly used in the biological sciences. The user selects an appropriate model from a list of models from the site and selects an optimality criterion suitable for his/her purpose. The user then inputs design parameters pertinent to his/her specific problem and the site returns the optimal design. Details of the construction of the optimal design and their justifications are not provided on the site but references to the source and other pertinent papers are provided at the bottom of the web page where results are displayed.

The site also has a desirable feature that it evaluates the efficiency of another design for comparison. Here and elsewhere, the usual definition and interpretation of efficiency is used.

Specifically, efficiency of a design is defined relative to the optimal design and standardly is the ratio or some function of the ratio of the two criteria values to facilitate interpretation. In particular, a design with 0.5 or 50% efficiency means that the design needs twice as many observations for it to do as well as the optimal design in terms of the criterion value. This additional feature is useful. For example, the optimal design can have fewer design points than the researcher likes. With a few strokes on the keyboard, the researcher can quickly explore having additional number of points and where they are to arrive at a design that seems more appropriate for his/her purpose. The implemented design should not stray too far from the optimum as measured by its efficiency, otherwise the chosen design may lose a lot in terms of statistical efficiency. This particular feature should also enable the user to easily evaluate robustness properties of the design to model assumptions before implementation and therefore empower the user to make an informed choice of a design.

The web site is housed at University of California at Los Angeles in the Department of Biostatistics at <http://optimal-design.biostat.ucla.edu/optimal/>. An earlier web site at <http://www.optimal-design.org/optimal/Home.aspx> was established at the State University of New York at Stony Brook but it has now moved and expanded to the present site at UCLA. This web site seems to be the first of its kind aimed for practitioners interested to generate optimal designs for commonly used models in the biological sciences. Many of these models are used in other disciplines as well so the site may appeal to researchers in other fields too. For instance, the Michaelis-Menten model is also used in botany or in conservation biology (Clench, 1979). An important feature of the web site is that it evaluates efficiency of any user-supplied design and so enables researchers to make an informed decision on the choice of a design.

There are six main pages on the web site. The opening page provides an indication what the site tries to accomplish and the Introduction page gives background, including an introduction of the various concepts commonly used in the optimal design literature. It also provides a simple motivating example of an optimal design and the various common types of optimal designs used in practice. The publication page lists selected publications from the literature broken down by subtopics to help the visitor finds some references for the topic quickly. This page does not pretend to have a comprehensive list; just a sample of papers in each of the design topics. The "about us" page describes the key people who helped put the web site together. The "faq" page lists several frequently asked questions with answers.

The main substance of the site is on the page entitled "web based design programs". This page lists many commonly used models and for each type of models, several types of optimal designs for the visitor to select from. They include polynomial regression models, Fourier regression models, Miscellaneous design problems, Nonlinear regression models that include the Weibull model, Richards model, Emax model, Michaelis-Menten models, Inverse Quadratic model and the Logistic model. More specialized topics follow including specific models described in selected papers. For example, under the subheading Dose Finding Toxicity Model, there is material taken from Dette, et al. (2009) where they considered optimal designs for a toxicity study.

4.1 Demonstrations

We now demonstrate how to find the D-optimal design for the homoscedastic quadratic model on the interval $[0, 3]$ in Example 2 using the web site at <http://optimal-design.biostat.ucla.edu/optimal/>. After this simple demonstration, we also find two other types of optimal designs for this model.

- a. It was claimed that the D-optimal design for the quadratic model is equally supported at 0, 1.5 and 3. To obtain this result from the web site, we first visit the

above web page and click on the heading "web-based design programs". Then select PSI(p)-optimal design from the Polynomial Regression Models subheading and note that the optimality criterion PSI with $p = 0$ corresponds to D-optimality. Accordingly, we type 0 and 3 in the Design interval Box, select 2 from the drop down menu from the "Polynomial degree d" box and select $p = 0$ for the third box (see Figure 1). If we hit return after these data are entered, the returned design is equally supported at 0, 1.5 and at 3. Its D-optimality is confirmed by the equivalence theorem through examining the shape and form of the equivalence plot expected when the design is optimal (see Figure 2). What is the D-efficiency of the design equally supported at 5 uniformly spaced points? To answer this question, we check the box "Additional Options" and input 0, 0.75, 1.5, 2.25 and 3 in the "User design points" and input 0.2, 0.2, 0.2, 0.2, 0.2 in the "User corresponding weights" box. The order of these weights must correspond to the design points specified earlier. Alternatively, to simplify the task, one may also input 1, 1, 1, 1, 1 instead of their actual weights and the code will automatically scale them to sum to unity. Upon hitting return, the site returns a D-efficiency for this 5-point uniform design, which is about 45%. This simple example shows that the popular uniform designs may not always perform well and having more points does not always guarantee higher efficiencies. Both Figures 1 and 2 are screen shots from the web site that show the input boxes, the equivalence plot and the results.

Notice that Figure 2 shows the equivalence plot meets the conditions required for an optimal design; the plot is bounded above by one with equality at the support points. As with all web pages under the "web-based design programs" heading, the references at the bottom of the page give the theoretical justification of the optimal design and references under "Additional References" provide further useful information.

- b. Suppose now we wish to determine the locally optimal design for estimating the turning point. We click on the subheading "Bayesian design for estimating the turning point of a quadratic regression". Two types of optimal designs are offered; the first is a ϕ -optimal design and the second is a B-optimal design, with B standing for Bayesian. Suppose we wish to find the locally ϕ -optimal design for estimating the turning point on the design interval is $X = [0, 3]$ and the nominal values for the two parameters are given by $\beta_1 = 1 = \beta_2$. First we click on the button to select the design criterion, and after data input, we hit return to obtain the locally optimal design for estimating the turning point. This design is locally supported at 0, 1.5 and 3 and the optimum weights are 0.344, 0.500 and 0.156. Again the equivalence plot has the right shape and form, confirming that the generated design estimates the turning point in the quadratic with the smallest variance among all designs on the interval $X = [0, 3]$. A similar plot can be shown along with the references for the construction of the optimal design but we omit them for space consideration.
- c. Suppose we now have prior information on the location $g(\cdot)$ of the turning point in the form of a prior density and believe it has user-selected first two moments, say equal to 0.5 and 1 respectively. For this situation, the web site can produce the Bayesian-optimal design for estimating the turning point by clicking on the B-optimal Design button on the same page first before inputting the required parameters. The returned design is supported at 0, 1.524 and 3. The proportion of observations to take at each of these points is 0.351, 0.481 and 0.167 respectively. As before, the equivalence plot of this design is automatically displayed following the claimed results and its shape confirms that the design is indeed Bayesian-optimal.

Further demonstrations on how to use the tools on the site to generate optimal designs for nonlinear models useful for toxicity studies are given in Berger and Wong (2009). Clearly, more design questions can be asked to reflect other practical concerns. For space considerations, we describe two examples. The first concerns finding an optimal design when there may be heteroscedasticity in the model. This is generally a difficult question to answer because the variance of the response now depends on where the response is observed and frequently the variance structure is unknown in practice. If one is willing to assume that the variance structure can be modeled using one of the functional forms listed on another web page under the subheading "Locally D-optimal Designs for Models with Partially Specified Heteroscedastic Structure", then corresponding D-optimal designs for the heteroscedastic polynomial models can be generated and compared with competing designs using D-efficiencies.

The second example concerns multiple objective optimal designs, which is currently only available on the web site in a very limited form. This situation arises frequently in practice when there are more than one goal in the study and each goal may be more or less important than others. For instance, many biological models have some parameters more interesting than others. As another example using the quadratic model, estimating the turning point may be the primary goal and the secondary goal is to find a D-optimal design to estimate all three parameters. Construction of such a multiple-objective optimal design requires that the goals be first prioritized in terms of their importance and the user specifies minimum efficiency sought for each objective, with more important ones having higher efficiencies. Such a constrained optimization design problem is then solved using compound optimal designs described in Cook and Wong (1994) and Wong (1999). Illustrative applications of multiple objective designs for biomedical studies are available in Huang and Wong (1998), Zhu et al. (2000) and, Zhu and Wong (2000a, b, 2001).

4.2 Lessons Learned

Setting up such a web site is useful and follows the current technology trend. However, the construction and maintenance of such a web site are both laborious and costly. It is team work and the team should comprise researchers knowledgeable in the theory and applications of optimal designs and people with ability to write good codes, perform interface work and implement programming codes on the web site. Usually the latter set of researchers or students come from the Department of Applied Mathematics or Computer Science. Our team began work on this site in 2006 and already the technology used to construct the site is now quite obsolete and can benefit greatly with a total reconstruction using the latest technology. All investigators agreed to use MATLAB to write the source codes and it worked well for a while. A continuing problem that the team has is that when MATLAB has a new version, some of the earlier source codes may not work well and they have to be updated using newer command codes. This then requires the team to revisit and replace program codes periodically - a problem not anticipated before the start of the project. The major problem with such a project is that it is costly and when the funding from the grant expires, updates, improvement and the expansion of the web site also stop. This means that there should be a long term plan and commitment to manage and run the site well.

Another time-consuming task the team encountered in the creation of the web site is that when results are being consolidated from the literature, there were cases where results turned out to be piecemeal. Some authors had only partial results for their problems published and the team had to work to fill in results for the invariably more difficult cases. The team was successful in doing so for several cases, reinforcing that researchers with strong technical skills have to be included in such a team.

5 Summary

The field of optimal experimental designs appears esoteric to some in the statistical community and much more to the practitioners. While the general theory for constructing continuous optimal designs provides a unified approach, specific details have to be worked out for each model. The calculation can be involved and it is helpful to have a web site that produces the optimal design with a few keystrokes after the user inputs the design parameters for a specific problem. Such a web site should facilitate research, pique interest and attract new and novice researchers to the field and at the same time, enable practitioners to have easier access to optimal designs, which in turn may encourage them to exercise greater care in designing future experiments.

As always, a cautionary note is that an optimal design should not be used religiously but more as a guide or benchmark. This is because the optimal design is found under a fixed set of assumptions that may not adequately reflect reality and so may not satisfy the needs of the practitioners. For example, the optimal design may have a singular information matrix and if the practitioner wants to estimate all parameters, then such an optimal design is not appropriate. Different optimal designs under various settings should be compared carefully before arriving at the implemented design. The guiding principle is that the implemented design should not stray too far from the optimum as measured by its efficiency relative to the optimum. The web site facilitates this calculation and hopefully more informed designs will be implemented in practice using this and hopefully more other such sites in the future.

Acknowledgments

I thank my co-investigators Professor Dette Holger from Ruhr-Universitaet Bochum, Germany, Professor Wei Zhu from State University of New York at Stony Brook and several doctoral students who wrote codes and implemented them on the web site. These students are acknowledged on the web site and a few of them are now young professionals in the field. I thank Dr. Andrey Pepelyshev from the University of Cardiff, England for writing several late stage codes for the site. I also wish to thank four consultants who had provided valuable comments on the web site. They are Professor Martijn Berger from the Department of Methodology and Statistics at The University of Maastricht in The Netherlands, Professor William Rosenberger from the Department of Statistics at George Mason University, Professor Joan Hilton from the Division of Biostatistics and Epidemiology at the University of California at San Francisco and Dr. Nikolay Strigul from the Department of Ecology and Evolutionary Biology at Princeton University.

Parts of this manuscript was written in December 2011 when I was a visiting fellow and scientific advisor for a six-month workshop on Design and Analysis of Experiments at The Sir Isaac Newton Institute at Cambridge, England in 2011. I would like to thank the Institute for the support during my repeated visits to the institute in the second half of 2011.

Role of the Funding Source

The construction of the website at <http://optimal-design.biostat.ucla.edu/optimal/> was entirely funded by a National Institute of General Medical Sciences grant award R01GM072876.

References

- Aigner DJ. A brief introduction to the methodology of optimal experimental design. *J of Econom.* 1979; 11:7–26.
- Atkinson AC. The usefulness of optimum experimental designs. *JRSS Series.* 1996; 58:59–76.
- Atkinson AC. Recent developments in the methods of optimum and related experimental designs. *Int Stat Rev.* 1998; 56:99115.
- Atkinson, AC.; Donev, AN.; Tobias, RD. Oxford Statistical Science Series. 2007. Optimum Experimental Designs, with SAS.
- Berger, MPF.; Wong, WK. Applied Optimal Designs. Chichester, West Sussex, England: John Wiley and Sons; 2005.

- Berger, MPF.; Wong, WK. An Introduction to Optimal Designs for Social and Biomedical Research. John Wiley and Sons; 2009.
- Bornkamp B, Bretz F, Dette H. Response-adaptive dose-finding under model uncertainty. *Annals of Applied Stat.* 2011; 5:1611–1631.
- Bretz F, Dette H, Pinheiro J. Practical considerations for optimal designs in clinical dose finding studies. *Stat in Med.* 2010; 29:731–742. [PubMed: 20213708]
- Chen RB, Wong WK, Li KY. Optimal minimax designs for estimating response surface over a pre-specified region in a heteroscedastic model. *Stat and Prob Let.* 2011; 78:1914–1921.
- Chernoff, H. CBMS-NSF Regional Conference Series in Applied Mathematics. 1972. Sequential Analysis and Optimal Design.
- Clench H. How to make regional lists of butterflies: some thoughts. *Journal of the Lepidopterists Society.* 1979; 3:216231.
- Cook RD, Nachtsheim CJ. A comparison of algorithms for constructing exact D -optimal designs. *Technometrics.* 1980; 22:315–323.
- Cook RD, Wong WK. On the equivalence of constrained and compound optimal designs. *JASA.* 1994; 89:687–692.
- Dette H, Bretz F. Optimal designs for dose-finding studies. *JASA.* 2010; 103:1225–1237.
- Dette H, Pepelyshev A, Wong WK. Optimal designs for dose finding experiments in toxicity studies. *Bernoulli J.* 2009; 15:124–145.
- Dette, H.; Studden, WJ. The Theory of Canonical Moments with Applications in Statistics, Probability and Analysis. John Wiley & Sons; 1997.
- Dette H, Wong WK. E-ptimal designs for the Michaelis-Menten models. *Statistics & Probability Letters.* 1999; 44:405–408.
- Dykstra O. The augmentation of experimental data to maximize $|XX|^{-1}$. *Technometrics.* 1971; 13:682–688.
- Fedorov, VV. Theory of Optimal Experiments. Academic Press; 1972.
- Fedorov VV, Hackl P. Model-oriented design of experiments. *Lecture Notes in Statistics.* 1997:125.
- Flournoy N, Rosengerber WF, Wong WK. New Developments and Applications in Experimental Design. Institute of Mathematical Statistics, Lecture Notes-Monograph Series 34. 1998; 1998
- Ian Ford, Ford I. Ph D Thesis. University of Glasgow; 1976. Unpublished
- Ford I, Kitsos CP, Titterington DM. Recent advances in nonlinear experimental design. *Technometrics.* 1989; 31:49–60.
- Hill DH. A review of experimental design procedures for regression model discrimination. *Technometrics.* 1978; 20:15–21.
- Huang YC, Wong WK. Multiple-objective optimal designs. *J of Biopharm Stat.* 1998; 8:635–643. [PubMed: 9855039]
- Kiefer, J. Jack Carl Kiefer Collected Papers III: design of experiments. New York: Springer-Verlag; 1985.
- King J, Wong WK. Optimal minimax designs for prediction in heteroscedastic models. *Journal of Statistical Planning and Inference.* 1998; 69:371–383.
- King J, Wong WK. Minimax D -optimal designs for the logistic model. *Biometrics.* 2000; 56:1263–1267. [PubMed: 11129489]
- Matthews, JNS.; James, PW. An optimal design in the measurement of cerebral blood flow using the Kety-Schmidt technique. In: Berger, MPF.; Wong, WK., editors. *Applied Optimal Designs.* John Wiley & Sons, Ltd; 2005.
- McPhee, J.; Yeh, WG. Optimal experimental design for parameter estimation and contamination plume characterization in groundwater modeling. In: Berger, MPF.; Wong, WK., editors. *Applied Optimal Designs.* John Wiley & Sons, Ltd; 2005.
- Mentre F, Mallet A, Baccar D. Optimal design in random-effects regression models. *Biometrika.* 1997; 84:429–442.
- Mentre F, Escolano S. Prediction discrepancies for the evaluation of nonlinear mixed effects models. *J Pharmacokin Pharmacol.* 2006; 33:345–367.

- Mitchell TJ. An algorithm for the construction of D -optimal experimental designs. *Technometrics*. 1974; 16:203–211.
- Ogungbenro K, Graham G, Gueorguieva I, Aarons L. The use of a modified Fedorov exchange algorithm to optimize sampling times for population pharmacokinetic experiments. *Comp Meth and Prog in Biomed*. 2005; 80:115–125.
- Ouwens-Mario JNM, Tan Frans ES, Berger MPF. Maximin D -optimal designs for longitudinal mixed effects models. *Biometrics*. 2002; 58:735–741. [PubMed: 12495127]
- Pazman, A. *Foundations of Optimum Experimental Design*. D. Reidel Publishing Company; 1986.
- Pukelsheim, F. *Optimal Design of Experiments*. John Wiley; 1993.
- Rosenberger WF, Haines LM. Competing designs for phase I clinical trials: A review. *Stat in Med*. 2002; 21:2757–2770. [PubMed: 12228889]
- Schwabe, R. *Lecture Notes in Statistics*. Springer; 1996. *Optimum Designs for Multi-Factor Models*; p. 113
- Silvey, SD. *Optimal Design*. Chapman and Hall; 1980.
- Tekle FB, Tan Frans ES, Berger MPF. Maximin D -optimal designs for binary longitudinal responses. *Comput Stat & Data Anal*. 2008; 52:5253–5262.
- Wong WK. A unified approach to the construction of mini-max designs. *Biometrika*. 1992; 79:611–620.
- Wong WK. Recent advances in constrained optimal design strategies. *Stat Neerlandica*. 1999; 53:257–276.
- Wong WK, Cook RD. Heteroscedastic G -optimal designs. *JRSS, Series B*. 1993; 55:871–880.
- Wong WK, Lachenbruch PA. Designing studies for dose response. *Stat in Med*. 1996; 15:343–360. [PubMed: 8668866]
- Zhu W, Wong WK. Multiple-objective designs in a dose response experiment. *Journal of Biopharmaceutical Statistics*. 2000a; 10:1–14. [PubMed: 10709797]
- Zhu W, Wong WK. Optimum treatment allocation for dual-objective clinical trials with binary outcomes. *Communications in Statistics-Theory and Methods*. 2000b; 29:957–974.
- Zhu W, Zeng Q, Wong WK. Dual-objective Bayesian optimal designs for a dose-ranging study. *Drug Information Journal*. 2000; 34:421–428.
- Zhu W, Wong WK. Bayesian optimal designs for estimating a set of symmetric quantiles. *Stat in Med*. 2001; 20:123–137. [PubMed: 11135352]

Optimum Experimental Designs
WWW.OPTIMAL-DESIGN

home | introduction | web based design programs | publications | about us

Optimal Experimental Designs

PSI(p) Optimal Design for Polynomial Models

Brief description of the model:

We consider a univariate polynomial regression model of degree d given by $Y = f(x)^T \beta + \epsilon$. Here Y is the response, $f(x) = (1, x, \dots, x^d)^T$ is the vector of monomials up to degree d , $\beta = (\beta_0, \dots, \beta_d)^T$ is a vector of unknown parameters and each random error term with mean 0 and variance v . All errors are independent and identically distributed.

Optimal design sought:

Suppose that you want to find a good design to estimate the unknown parameters β in the univariate polynomial regression model. This program finds the optimal support points and their corresponding weights by numerically maximizing the means Φ_p , a design criterion proposed by Kiefer.

The values of p are non-positive and three common choices are :

- (1) $p = 0$: the so called D-optimality or determinant criterion
- (2) $p = -1$: the so called A-optimality or average variance criterion
- (3) $p = -\infty$: the so called E-optimality or smallest eigenvalue criterion

Please see the FAQ page for the rationale of difference choices of p .

Parameters to be input:

Design interval = 0,3 .

Polynomial degree $d = 2$.

Select the type of optimality you are interested in by specifying the value of p : $p = 0$.

What you get in the output:

1. The PSI(p)-optimal design.
2. A plot of the derivative function for the PSI(p)-optimal design.

Additional options:

You may also supply a user defined design to compare its efficiency with the optimal design. Please note that your input must have at least $d + 1$ support points; otherwise, the input design has a singular information matrix and an error message will appear.

☒ Check this box if you would like to compute your design efficiency, and specify your design below.

User design points: 0,0.75,1.5,2.25,3 (*please separate the values by ',').

User corresponding weights: .2,.2,.2,.2 (*please separate the values by ',').

*Please make sure the weights correspond to the design points.

*The sum of the weights should be 1; otherwise we will normalize them for you.

Design Results

polynomial degree = 2

matrix mean optimality criterion $p = 0$

Figure 1.

A screen shot of the output from the web page for Example 4.1(a).

design interval = [0,3]

YOUR DESIGN IS

design points = [0.000,0.750,1.500,2.250,3.000]
 design weights = [0.200,0.200,0.200,0.200,0.200]
 efficiency = 0.45391

THE OPTIMAL DESIGN IS

design points = [0.000,1.500,3.000]
 corresponding weights = [0.333,0.333,0.333]

References

References for the construction of the optimal design:

Kiefer, J. (1959). Optimum Experimental Designs (with discussion). *Journal of the Royal Statistical Society, Ser. B.*, 21.
 Pukelsheim, F. (1993). *Optimal Design of Experiments* (chapter 6). John Wiley.

Additional references:

Detle, H. and Studden, W. J. (1997). *The Theory of Canonical Moments with Applications in Statistics, Probability, and* John Wiley.
 Pazman, A. (1986). *Foundations of Optimum Experimental Design*. D. Reidel Publishing Company.

Figure 2.

A screen shot of the output from the web page for Example 4.1(a) (cont'd).