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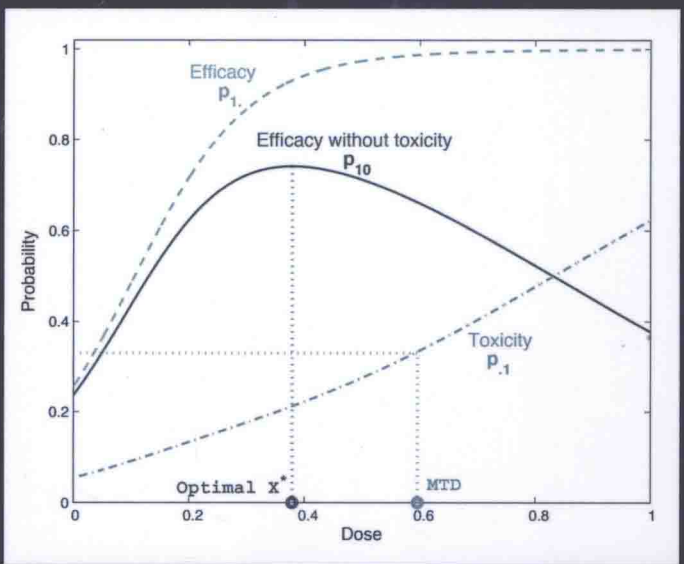
Optimal Design for Nonlinear Response Models



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Symbol Description

$y, \boldsymbol{y}$	response or independent or observed variable
$\eta, \boldsymbol{\eta}$	response function
$x, \mathbf{x}$	independent or control or design or regressor variables, predictors
$z, \mathbf{z}$	uncontrolled regressor variables, covariates
$\theta, \boldsymbol{\theta}$	parameters
m	number of parameters
$\boldsymbol{\Theta}$	parameter space
$\mathbf{f}(\mathbf{x})$	vector of basis functions
$\eta(\mathbf{x}, \boldsymbol{\theta})$	response function
$\varepsilon, \boldsymbol{\varepsilon}$	(response) error
σ^2	variance of the error
ξ_n	discrete design
$\xi, \xi(d\mathbf{x})$	continuous design
ξ^*	optimal design
Ξ	set of designs
$x_i, \mathbf{x}_i$	design support points
$\mathfrak{X}$	support (design) region
r_i, n_i	number of observations at $\mathbf{x}_i$
p_i, w_i	weight of observations at $\mathbf{x}_i$
n	number of support points
N	total number of observations
$\mathbf{M}$,$\mathbf{M}(\xi)$	normalized information matrix
$\underline{\mathbf{M}}$	nonnormalized information matrix
$\boldsymbol{\mu}(\mathbf{x}, \boldsymbol{\theta})$	Fisher information matrix
$\mathbf{D}$, $\underline{\mathbf{D}}$	dispersion matrix of estimators $\hat{\boldsymbol{\theta}}$
$d(\mathbf{x}, \xi)$	normalized variance of predicted response $\eta(\mathbf{x}, \hat{\boldsymbol{\theta}})$
Ψ,$\Psi(\mathbf{M})$	optimality criterion
$\boldsymbol{\Omega}$	variance-covariance matrix of random parameters
$\varphi(\mathbf{x}, \xi)$	sensitivity function for design ξ at $\mathbf{x}$
$\phi(\mathbf{x})$	penalty/cost function at $\mathbf{x}$
$\Phi(\xi)$	total penalty/cost for design ξ

Preface

Our main intent is to introduce the reader to the statistical area that in rather loose terms can be called "model-based optimal design of experiments." The word "design" implies that there exist some variables, the values of which can be chosen in the planning stage. We focus our exposition on cases when a researcher can describe the relation between these variables and responses (response variables) by means of a mathematical model that describes the observed system. Often the system description is based on the deterministic model while the observational component is modeled via stochastic mechanisms. However, it is not always the case: biological systems or clinical trials are good examples of when stochastic models can be used for system description as well. See, for instance, examples in Section 7.4 where stochastic differential equations are used to model intrinsic patient variability in pharmacokinetic studies. Regression models with random parameters provide another example of such a setting.

Both authors spent more than a decade in the pharmaceutical industry developing the optimal design machinery for earlier phases of clinical studies. This explains why the majority of examples are related to biopharmaceutical applications; see earlier survey papers by Fedorov and Leonov (2005) [144], Fedorov et al. (2007) [133]. Nevertheless, we would like to emphasize that the potential applications are much wider. The main distinction of this monograph from many others published recently is the strong emphasis on nonlinear with respect to unknown parameters models. Still, the exposition of key ideas of optimal experimental design is much simpler and more transparent for linear models. That is why the reader will find rather extensive introductory material that is devoted to the linear case.

The book is intended for graduate students and researchers who are interested in the theory and applications of model-based experimental design. The main body of the book requires a modest formal background in calculus, matrix algebra and statistics. Thus the book is accessible not only to statisticians, but also to a relatively broad readership, in particular those with backgrounds in natural sciences and engineering.

We would like to express our gratitude to the many colleagues with whom we have collaborated on various optimal design problems over recent years, in particular Alexander Aliev, Vladimir Anisimov, Anthony Atkinson, Brian McHugh, Vladimir Dragalin, Nancy Flournoy, Bob Gagnon, David Gruben, Agnes Herzberg, Byron Jones, Mindy Magee, Sam Miller, Viacheslav Vasiliev,

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Introduction

Over the next few pages we provide a rather sketchy and likely subjective overview of the evolution of optimal experimental design. With advances of the Internet, more facts can be found online. As far as authors' preferences are concerned, the first author would "Google" the Web, while the second author would be "Yahooing."

Stigler (1974) [368] provides exciting reading on the early "formalized" attempts of optimal design of experiments. The first well-documented contribution to optimal design theory was made by Kirstine Smith (1918) [364]. She explored the regression problem for univariate polynomials of order up to six, with the control variable varying between -1 and 1. The observational errors were independent, identically distributed and additive. Smith found designs that minimize the maximum variance of prediction over the design region (later called G-optimal). Other designs were considered, for example uniform designs, and the effect of nonconstant variance was investigated. Smith's paper thus had all the components needed to specify an optimal design: a response model, a design region, a design criterion, specification of observational errors and a comparison of optimal designs with designs that are popular among practitioners. Smith's paper was all but forgotten for nearly 40 years.

Wald (1943) [391] started the comparison of designs using values of noncentrality parameters for tests of hypotheses about parameters defining a response model. This problem led him to the necessity of comparing the determinants of the information matrix, i.e., to D-optimality. The close relation of the D-criterion with Shannon's information was explored by Lindley (1956) [258] in the Bayesian setting. Very soon this criterion became one of the most used (and sometimes abused) criteria in design theory. Guest (1958) [184] showed that support points of the G-optimal design for the polynomial of order m coincide with roots of the derivatives of the $(m-1)$-th Legendre polynomial together with the end points. Hoel (1958) [201] constructed D-optimal designs and commented that his designs were the same as those of Guest. Two years later Kiefer and Wolfowitz (1960) [232] proved the equivalence of G- and D-optimality and started to treat experimental design as a particular area of convex optimization theory. The latter direction was explored by Karlin and Studden (1966) [225] and by Fedorov (1969, 1972) [125], [127].

Jack Kiefer undoubtedly was the main contributor to the development of the core of optimal design theory in the 1950s and 1960s. For a survey and

collection of his papers on optimal design, see Wynn (1984) [418] and Brown et al. (1985) [57].

Elfving (1952) [114] gave a geometrical interpretation of optimal designs and introduced a criterion that became known as A-optimality (average variance of regression parameter estimators). He found that the points of the optimum design lie on the smallest ellipsoid that contains the design region, an insight further developed by Silvey and Titterington (1973) [361]. Elfving's results were almost immediately extended to D-optimality by Chernoff (1953) [70] who also introduced the concept of locally optimal design for nonlinear regression models; see Chernoff (1972) [71]. This concept will be used rather extensively in our book.

Box and Lucas (1959) [54] used the results of Chernoff, Elfving, and Wald to find locally D-optimal designs for nonlinear models arising in chemical kinetics. Box and Hunter (1965) [53] developed an adaptive strategy for updating the design one trial at a time as observations become available. They extended Lindley's result [258] for the Bayesian justification of D-optimality and provided a derivation of the best conditions for the next trial. The approach based on the use of the Shannon information measure was further developed by Klepikov and Sokolov (1961) [234] and elaborated by Fedorov and Pazman (1968) [150], Caselton and Zidek (1984) [63], Caselton et al. (1992) [62], and revisited by Sebastiani and Wynn (2000) [354].

Box and Hunter (1965) [53] proved that to maximize the decrement of the determinant of the variance-covariance matrix of estimated parameters, observation(s) should be done at the point where the variance of prediction of the linearized model attains its maximum. It is a short step to consider the same "adaptive" procedure for linear models and to observe that optimal designs are independent of parameter values, and so to obtain the algorithm for the iterative construction of optimal designs. This idea was earlier introduced by Klepikov and Sokolov (1961, 1963) [234], [365], [366] who used the term "continuous" design, which in the modern setting corresponds to the first-order algorithm with constant (but very small) step length. The further development of iterative construction of optimal designs was accomplished by Fedorov (1971, 1972) [126], [127], Wynn (1970, 1972) [416], [417], Fedorov and Malyutov (1972) [148], Atwood (1973) [25], Tsay (1976) [385], Wu and Wynn (1978) [409], Wu (1978) [408]. These results triggered a series of publications on numerical methods of optimal design construction; cf. Mitchell (1974) [286], Fedorov and Uspensky (1975) [151], Titterington (1976) [375], Silvey et al. (1978) [362], Torsney (1983) [380], Nachtsheim (1987) [293], Atkinson and Donev (1992) [19], Gaffke and Mathar (1992) [166], Atkinson et al. (2007) [24].

If several models are of interest, the standard criteria can be extended to compound criteria that are weighted linear combinations of standard criteria and to which the standard convex design theory applies; see Atkinson and Cox (1974) [18], Läuter (1974) [249]. If interest lies solely in choosing one model out of two or more competing models, the T-optimum designs of Atkinson and

Fedorov (1975a,b) [21], [20] address the discrimination problem in the "frequentist" setting. Equivalence between model discrimination problems and parameter estimation problems was initially discussed in Wald (1943) [391]; Fedorov and Khabarov (1986) [140] proved the equivalence of these problems for a range of different criteria. Box and Hill (1967) [51] described a Bayesian procedure for discriminating between models that leads to the sequential updating of the prior probabilities of the models. Fedorov and Pázman (1968) [150] developed an adaptive Bayesian procedure for simultaneous model discrimination and parameter estimation.

Special types of optimal design problems arise in environmental studies, with spatial- and longitudinal-type experiments. In both cases the assumption of independence does not hold, and one has to take into account the dependence between observations introducing various models for covariance functions. Problems of optimal allocations or optimal sampling in the case of correlated observations happened to be mathematically rather difficult. First attempts at constructing optimal sampling schemes in the optimal design setting were done by Sacks and Ylvisacker (1966, 1968a,b) [347], [348], [349] in a series of publications where they proposed asymptotically optimal allocations. Cambanis (1985) [59], Matérn (1986) [270], Megreditchan (1979) [274], Micchelli and Wahba (1981) [282] developed various aspects of optimal spatial allocations. Summaries of results in that area can be found in Fedorov (1996) [131], Guttorp et al. (1993) [185], Martin (1996) [268], Fedorov and Hackl (1997) [135], Müller (2007) [291].

The first comprehensive volume on the theory of optimal experimental design was written by Fedorov (1969, 1972) [125], [127]. Silvey (1980) [360] gave a very compact description of the theory of optimal design for estimation in linear models. Other systematic monographs were published by Bandemer et al. (1977) [30], Ermakov (1983) [115], Pázman (1986) [306], Ermakov and Zhigljavsky (1987) [116], Pilz (1991) [309], Atkinson and Donev (1992) [19], Pukelsheim (1993) [328], Schwabe (1996) [353], Fedorov and Hackl (1997) [135], Wu and Hamada (2002) [414], Melas (2006) [275], Atkinson et al. (2007) [24], Berger and Wong (2009) [44], Morris (2010) [289], Goos and Jones (2011) [180], Rasch et al. (2011) [335], Pronzato and Pázman (2013) [322].

We do not discuss factorial experiments in this book. While there are a lot of intersections between "model-based design of experiments" and "design of factorial experiments," the differences are mainly in models and methods of optimal design construction. In the latter case, these are primarily combinatorial and algebraic methods; see Fisher (1971) [157], Wu and Hamada (2002) [414], Bailey (2008) [29].

While the focus of our monograph is on nonlinear models, we always start the exposition of key ideas for linear with respect to unknown parameters models. Then we move toward linearization of models, locally optimal estimators and designs, and after that proceed to multi-stage and adaptive designs. In discussing adaptive procedures, we use those that are stopped when the sample size (number of observations) reaches the predetermined value. Often

this stopping rule is called "noninformative stopping" compared to "informative stopping" when the rule depends on the observed responses and/or current values of estimators.

Models and optimization problems. In the description of experiments we distinguish between *dependent*, or *response* variables that are altered by the change in the experimental conditions, and *independent*, or *predictor* variables that describe the conditions under which the response is obtained. The former variables are usually denoted by y. For the latter we distinguish between variables x that are controlled by the experimenter, and variables z, often called *covariates* that are not, such as weather conditions in meteorology or some of a patient's physical and physiological characteristics in clinical studies. Dependent and independent variables are often vectors that we highlight by using a boldface font, as in $\mathbf{y}$, $\mathbf{x}$ and $\mathbf{z}$.

The set of values of control variables at which the response variable may be observed is called a design region $\mathfrak{X}$. Usually, $\mathfrak{X}$ is a finite set with a dimension corresponding to the number of design variables. More generally, $\mathfrak{X}$ can be a set in the functional space. The structure of $\mathfrak{X}$ is often not essential for major theoretical results in optimal design theory, while the computational aspects can be quite challenging.

Various design constraints are often encountered in practice. In a time-series context, it is typically not possible to have multiple observations at the same time point. Similar restrictions may be imposed due to geographical conditions, mixing constraints, etc. Among the most common causes for constraints are cost limitations and ethical concerns. For instance, the number of patients enrolled in a clinical study of a new drug depends on the study budget. In pharmacokinetic studies the number of drawn blood samples is often limited, in particular when drugs are investigated in special populations (e.g., in pediatric studies). Ethical, cost or any other constraints are quantified by the introduction of respective penalty functions together with inequalities that define their admissible values.

Once the response, control variables, and a model that links them are selected, a researcher should quantify the study objectives and constraints. Typically, objectives are described by a utility function and a particular criterion of optimality. In dose-finding studies, probability of efficacy without toxicity provides an example of the utility function, while the variance of the estimator of a dose that maximizes this probability may be selected as an optimality criterion. In classical design theory, a standard objective is the estimation of unknown parameters that define the response model; optimality criteria are scalar functions of the variance-covariance matrix of parameter estimates. Cost is proportional to the number of observations and has an upper bound.

Through decades of evolution optimal design theory extended in many directions adding more complex models and new types of problems to the traditional regression models and parameter estimation problem. We start the

exposition with standard regression models and then proceed with various extensions, which include, among others, multiresponse regression, regression models with random coefficients, and models described by stochastic differential equations. The latter two types of models add an intrinsic component of variability to the observational errors. Selection of the most informative variables discussed in Chapter 9 provides an example where traditional methods of optimal experimental design are applied to problems arising in observational studies.

Illustrating Examples

As noted earlier, the main ideas of optimal experimental design may be applied to a large number of problems in which both response and control variables have rather complicated structures. Here we outline a few examples; for details, see Chapters 6 – 9.

Dose-response studies. Dose-response models arise in clinical trials, either with a categorical outcome (e.g., success – failure as a response to the new experimental treatment, or disease progress on an ordinal scale) or continuous response (e.g., studies of pain medications when patients mark their pain level on a visual analog scale). In these examples, x represents the dose of a drug administered to the patient. The design problem may be formulated as finding those doses, within the admissible range, that provide the most accurate estimation of model parameters or utility functions given the sample size; see Chapters 6 and 8. In a more complex setting, the design variable x represents a dosing regimen (e.g., drug amount and frequency of drug administration).

Bioassay studies. Multiparameter logistic models with continuous response, sometimes referred to as the $E_{\max}$ or Hill models, are widely used in bioassay studies. Examples include models that relate the concentration of an experimental drug to the percentage/number of surviving cells in cell-based assays or models that quantify the concentration of antigens/antibodies in enzyme-linked immunosorbent assays (ELISA). In this context, the design variable x represents the drug concentration level; see Sections 6.3, 6.3.1, 8.1 for details.

Clinical PK studies. Multiple blood samples are taken in virtually all clinical studies, and the collected data are analyzed by means of various PK compartmental models. This leads to quite sophisticated nonlinear mixed effects models, which are discussed in Chapter 7. In these models $\mathbf{x}$ and $\mathbf{y}$ are k-dimensional vectors that represent sequences of k sampling times and respective observations for a particular patient.

Penalized or cost-based designs. In the previous example (PK studies) it is quite obvious that each extra sample provides additional information.

On the other hand, the number of samples that may be drawn from each patient is restricted because of blood volume limitations and other logistic and ethical reasons. Moreover, the analysis of each sample is associated with monetary cost. Thus, it makes sense to incorporate costs and other constraints in the design; see Chapter 4. In dose-finding studies exposure to high doses of an experimental drug may increase chances of toxicity, while exposure to low doses may deprive the patient of a potential cure. Both outcomes are associated with medical ethics. The objective of optimal design is to provide a quantified compromise between the ethics and the informativeness of the study. Examples of cost-based and constrained designs are provided in Sections 6.4, 6.5, 7.2, 7.3, 8.2, 8.3, and 9.2.

The structure of the book is as follows. In Chapter 1 we start with linear regression and least squares estimation and introduce relevant objects and problems of optimal design. At the end of Chapter 1 we focus on the maximum likelihood estimator and discuss estimation methods for nonlinear regression models. Convex design theory is the subject of Chapter 2. Numerical methods of the construction of optimal designs are dealt with in Chapter 3, and constrained/cost-based designs are considered in Chapter 4. In Chapter 5 we bridge earlier results to the case of nonlinear regression models where optimal designs depend on values of unknown parameters. In Chapters 6 – 9 we discuss the application of optimal design theory in biopharmaceutical problems. Chapter 6 is devoted to dose-response models while Chapter 7 addresses the application of optimal design in pharmacokinetic (PK) and pharmacodynamic (PD) studies and includes a description of the MATLAB®-based library for the construction of optimal sampling schemes for PK/PD models. Adaptive model-based designs are discussed in Chapter 8. Chapter 9 presents several examples of nontraditional applications of optimal experimental design. A list of potentially useful formulae from matrix algebra and matrix differential calculus is given in Chapter 10.

Computations for all examples were performed using various software platforms: MATLAB, SAS®, and R. For further details, see Chapters 6 – 9.

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