Estimation and optimal designs for multi-response Emax models

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Abstract

This thesis concerns optimal designs and estimation approaches for a class of nonlinear dose response models, namely multi-response Emax models. These models describe the relationship between the dose of a drug and two or more efficacy and/or safety variables. In order to obtain precise parameter estimates it is important to choose efficient estimation approaches and to use optimal designs to control the level of the doses administered to the patients in the study.

We provide some optimal designs that are efficient for estimating the parameters, a subset of the parameters, and a function of the parameters in multi-response Emax models. The function of interest is an estimate of the best dose to administer to a group of patients. More specifically the dose that maximizes the Clinical Utility Index (CUI) which assesses the net benefit of a drug taking both effects and side-effects into account. The designs derived in this thesis are locally optimal, that is they depend upon the true parameter values. An important part of this thesis is to study how sensitive the optimal designs are to misspecification of prior parameter values.

For multi-response Emax models it is possible to derive maximum likelihood (ML) estimates separately for the parameters in each dose response relation. However, ML estimation can also be carried out simultaneously for all response profiles by making use of dependencies between the profiles (system estimation). In this thesis we compare the performance of these two approaches by using a simulation study where a bivariate Emax model is fitted and by fitting a four dimensional Emax model to real dose response data. The results are that system estimation can substantially increase the precision of parameter estimates, especially when the correlation between response profiles is strong or when the study has not been designed in an efficient way.

Keywords: multi-response Emax models, Clinical Utility Index (CUI), optimal designs, system estimation, dose-response studies

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To my family and friends

List of Papers

The following papers, referred to in the text by their Roman numerals, are included in this thesis.

PAPER I: Magnusdottir, B.T.: Optimal designs for finding the dose that maximizes a Clinical Utility Index. *Submitted* 2014.

PAPER II: Magnusdottir, B.T.: Optimal design problems for the bivariate Emax model. *Research Report, Department of Statistics, Stockholm University* 2014. A shortened version of this paper has been published see [1].

PAPER III: Magnusdottir, B.T. and Nyquist, H.: Simultaneous estimation of parameters in the bivariate Emax model. *Submitted* 2014.

PAPER IV: Magnusdottir, B.T.: Optimal designs for a multi-response Emax model and efficient parameter estimation. *Research Report, Department of Statistics, Stockholm University* 2014.

Contents

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1. Introduction

Finding a suitable dose and, more generally, characterizing a dose response relationship is among the most difficult tasks during clinical development of a new drug. In dose response studies a primary response variable is usually defined, often an efficacy variable. However, information on the dose response relationship on safety is at least equally important as to that on efficacy. When response variables have been selected, dose response models can be used to describe the relation between dose and the response variables. It is important that the model parameters are estimated with as high precision as possible. The more data at hand the more precise parameter estimates can be obtained. Choosing a good and efficient estimation approach is also important for obtaining precise parameter estimates. Finally, in order to obtain precise parameter estimates, whenever possible, an optimal design should be used to control the level of the experimental variables which for dose response studies is the level of the drug.

Flournoy was one of the first to use optimal design theory for designing a dose response study in 1985 [2]. Since then optimal designs are used more and more frequently in dose response studies. Several authors have studied optimal designs when simultaneously considering an efficacy and a safety variable. Li, Durham, and Flournoy [3] and Dragalin and Fedorov [4] study designs where both responses are binary. Dragalin, Fedorov, and Wu [5] and Fedorov and Wu [6] study designs where the responses follow an underlying bivariate normal distribution but interest is in dichotomization for both responses. Fedorov, Wu and Zhang [7] also assume an underlying bivariate normal distribution but dichotomize only the safety response variable. In this thesis we are concerned with optimal designs where both the efficacy variable and the safety variable are continuous. Padmanabhan, Hsuan, and Dragalin [8] also consider optimal designs where both variables are continuous but their model and the aim of the study are different from what is assumed here. Finally we note that López-Fidalgo and Biswas [9] study designs allowing any general type of responses for both efficacy and safety and allowing the designs to depend on covariates such as age and sex. López-Fidalgo and Biswas, moreover, give a comprehensive discussion and references on optimal designs for dose response studies where efficacy and safety are considered simultaneously.

The primary aim of this thesis is to study optimal designs for specific dose response models, namely multi-response Emax models. Optimal designs are a class of study designs that are efficient with respect to some statistical criterion. In Section 3 we provide a brief introduction to optimal design theory. The theoretical material in Section 3 can be found in classical optimal design literature, in particular Atkinson, Donev and Tobias [10], Pázman [11] and Fedorov [12]. An aim of this thesis is to derive designs that are efficient for estimating the model parameters or a subset of the parameters. More specifically, to derive so called D- and D_s-optimal designs, respectively. Another aim is to study designs that are efficient when estimating the dose that maximizes the Clinical Utility Index (CUI). The Clinical Utility Index is a function that combines the efficacy and safety outcomes into a single metric in order to assess the net benefit from taking a specific dose of a drug. More information on the CUI is provided in the next section. In the optimal design literature designs that are efficient for estimating some function of the parameters are called c-optimal designs.

The problem of optimally designing studies for multi-response Emax models has, to our knowledge, not been studied earlier but the problem of optimally designing studies based on a single-response Emax model has been investigated by many authors see, for example Duggleby [13], Dette, Kiss and Bevanda [14], López-Fidalgo and Wong [15] and Dette, Kiss and Wong [16]. The reason why many have studied optimal designs for a single response Emax model is that this model is used widely in many distinct fields, in particular in biomedical sciences such as pharmaceutical science, biochemistry and in nutrition science. Moreover, this model is one of the most successful dose response models. A problem with optimal designs for the Emax model is that they depend upon unknown model parameters. This is a general problem with nonlinear models. For dose response studies there is usually some prior knowledge available from preclinical studies and/or comparator drugs. A design that is optimal, given a prior guess for the parameter values, is called a locally optimal design. In this thesis we consider only locally optimal designs but there is an extensive literature on methods dealing with the dependency of optimal designs on model parameters. These methods involve using so called sequential optimal designs, Bayesian optimal designs and minimax designs. A description of these methods can be found in e.g., Atkinson, Donev and Tobias [10]. When locally optimal designs are used in practice it is important to know how sensitive they are to misspecification of the prior parameter values. An important part of this thesis is to study the sensitivity of the derived optimal designs.

When data from a, hopefully well designed, dose response study has been collected we still have the issue of how to fit the chosen model to the data.

The second most important aim of this thesis is to study how to estimate the parameters in a multi-response Emax model. The most important estimation approach is Maximum Likelihood (ML) estimation upon which the optimal design theory relies. For multi-response models it is possible to derive ML estimates for each response profile separately as if the responses where independent. However, responses on the same patient are generally correlated and information in one relation could be useful when making inference in another relation. This motivates a simultaneous computation of ML estimates for the response profiles. Numerical methods for deriving ML estimates simultaneously for all response profiles in multi-response models are for example illustrated in Bates and Watts [17] and Marshall [18]. In this thesis we consider a multi-response Emax model and compare the precision of parameter estimates obtained from system estimation, when all parameters are estimated simultaneously, with the precision of parameter estimates obtained from equation-by-equation estimation, when the correlation structure between the relations is ignored.

The outline of this thesis is as follows. In Section 2, background information concerning the Emax model, the CUI and ML estimation is provided. Section 3 gives a brief introduction to optimal design theory and introduces the D-, D_s-, and c-optimal designs. Further, in Section 3 we provide some General Equivalence Theorem (GET) proofs. The GET is the main tool for deriving optimal designs. We also show some D-optimal designs for single response Emax models. In Section 4 a summary of the four papers is given and Section 5 provides an overall summary and suggestions for further research.

2. Background information

2.1 Estimation and Inference

Assuming additive errors, a model relating a response variable, y, to an explanatory variable, x, can be written in the general form

$$y(x) = f(x, \theta) + \varepsilon,$$

where f is a known function, θ is a vector of parameters and ε is a random error. All models considered in this thesis assume additive and normally distributed errors with mean 0. The most common method to estimate the parameters θ is the method of maximum likelihood (ML). The importance of ML estimators arises because of their appealing large sample properties; see for example, Ferguson [19]. Denote the ML estimators with $\widehat{\theta}_{ML}$ and the Fisher information matrix with $\mathbf{I}$,

$$\mathbf{I}_{i,j} = -\mathrm{E}\left[\frac{\partial^2}{\partial \theta_i \partial \theta_j} \log \phi(x, \theta) \middle| \theta \right],$$

where ϕ is the probability density function of the error term, ε. When the number of observations, N, is fixed the interest is on the standardized information matrix

$$M = \frac{1}{N}\mathbf{I}.$$

Under regularity conditions, ML estimators are both consistent and asymptotically efficient. Moreover, asymptotically we have that $\sqrt{N}\left(\widehat{\theta}_{ML} - \theta\right)$ is normally distributed with mean 0 and covariance M^{-1}.

For nonlinear models such as the Emax models, introduced in the following subsection, there is no closed formed expression for the ML estimates as in linear regression. Numerical procedures are needed to estimate the parameters. The Gauss-Newton procedure is an iterative algorithm that searches for the ML estimates of the parameters. The procedure involves linearizing the model using first order Taylor expansion about some initial guess θ_0 for the parameters. A new guess, θ_1 is derived by finding the ML estimates for the linearized model. The procedure is then repeated with θ_0 replaced by θ_1 and a

new estimate is found. This procedure is continued until a small change occurs between two successive parameter estimates.

2.2 Single- and multi-response Emax models

This thesis centers around Emax models. The Sigmoid Emax model, which is an Emax model with four parameters, was first introduced by A.V. Hill, see [20], to explain the binding of oxygen to hemoglobin. Since then it has been used to model various physicochemical reactions. Wagner [21] was the first to use the Sigmoid Emax model to explain the relationship between drug concentration and response. The rationale for his approach was based on receptor occupancy theory. Today the Sigmoid Emax model is widely used in pharmaceutical research when investigating how the effect of a certain drug depends on the dose. For an illustration of how the model is used in today's dose finding studies see, for example, Pinheiro et al. [22] and Miller, Dette, and Guilbaud [23]. The Sigmoid Emax model is of the form

$$f(x) = E_0 + E_{max}\frac{x^\gamma}{x^\gamma + ED_{50}^\gamma}.$$

In dose-response studies x stands for dose and $f(x)$ for the effect given dose x. An important feature of the Sigmoid Emax model is that the parameters have a natural interpretation. E_0 represents the effect when the dose is zero i.e. the placebo effect. E_{max} represents the maximal achievable effect from the drug after adjusting for the placebo effect. Further we see that $f(ED_{50}) = E_0 + \frac{1}{2}E_{max}$, so after adjusting for the placebo effect, ED_{50} is the dose that gives half of the maximal achievable effect. Finally γ, which is known as the Hill coefficient, determines the steepness of the response curve. In practice the effect of a drug usually increases monotonically with dose. If the maximum obtainable effect, E_{max}, is positive then a monotonically increasing Sigmoid Emax model is obtained by considering a positive Hill coefficient. The Sigmoid Emax model is sometimes simplified by setting $E_0 = 0$ and/or $\gamma = 1$. The model with $\gamma = 1$ is often called the Emax model. The model with $\gamma = 1$ and $E_0 = 0$ is often called the Michaelis-Menten model because it was proposed by Michaelis and Menten, see [24], who used it to model the relationship between velocity of a reaction and concentration of substrate. For more information on the properties of the Sigmoid Emax model and its mechanistic features see, e.g., Holford and Sheiner [25], Goutelle et al. [26], and Macdougall [27]. In this thesis we assume throughout that $\gamma = 1$, that is we work with the Emax model which we sometimes call the single-response Emax model in order to distinguish it from our multi-response Emax models.

The above model is one dimensional in the sense that it models the relationship between dose and a single response variable. In order to model how two or more response variables change with dose of a drug, we extend the Emax model to higher dimensions. In this thesis we consider multi-response Emax models were each dose response relation is modeled with an Emax model with $E_0 = 0$. For example, a model with two responses is written as

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} E_{max,1} \frac{x}{x+ED_{50,1}} \\ E_{max,2} \frac{x}{x+ED_{50,2}} \end{pmatrix} + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix},$$

where we assume that $\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix} \sim \mathcal{N}_2(0, \Sigma(\sigma_1, \sigma_2, \rho))$ is bivariate normally distributed. We refer to this model as the bivariate Emax model. The response variables can denote two efficacy variables, two safety variables or one of each of these. In the first two papers the two responses, y_1 and y_2, stand for an efficacy and a safety variable, respectively. Thus $E_{max,1}$ represents the maximal achievable effect and $ED_{50,1}$ is the dose giving half of the maximal effect. $E_{max,2}$ represents maximal realizable side-effect and $ED_{50,2}$ is the dose at which half maximal side-effect is obtained.

2.3 The Clinical Utility Index (CUI)

The Clinical Utility Index (CUI) is a tool for multiattribute decision making. While the effect of a drug usually increases with dose, too high a dose leads to problems with side-effects. The CUI models the patient net benefit from receiving a particular dose of a drug. The term and the use of the CUI in dose finding studies is relatively new, but the CUI is an increasingly popular tool in drug development. For a good historical overview of the CUI see, e.g., Carrothers et al. [28]. Although relatively new in drug development, functions that combine several outcomes into a single metric have a long history in industrial statistics, where the term 'desirability index' is used see, e.g., Harrington [29] and Derringer and Suich [30]. The form and derivation of the CUI should be considered separately for each drug under investigation. The most common approach is however to use a linear combination of the different response variables

$$\text{CUI}(x) = \sum_{\substack{\text{All efficacy} \\ \text{variables}}} v_j y_j - \sum_{\substack{\text{All safety} \\ \text{variables}}} v_k y_k.$$

As before x denotes the dose and here v_j represents the weight (importance) of variable y_j. The sums are over all efficacy/safety variables that are chosen to

be represented in the CUI. The variables chosen for the CUI should be those of most importance to the patients. Two highly correlated variables need not both be included in the CUI. For explicit examples of how linear CUI is used in practice see Ouellet et al. [31] and Khan, Perlstein and Krishna [32]. In this thesis we include a single efficacy and a safety variable in the CUI and use Emax models for both response profiles. When placebo effects are not modeled we define the CUI as

$$\begin{aligned}\mathrm{CUI}(x) &= v_1 y_1(x) - v_2 y_2(x) \\ &= v_1 E_{max,1} \frac{x}{x + ED_{50,1}} - v_2 E_{max,2} \frac{x}{x + ED_{50,2}}.\end{aligned}$$

A graphical representation is shown in Figure 2.1. In this thesis we consider c-optimal designs for estimating the dose that maximizes the CUI.

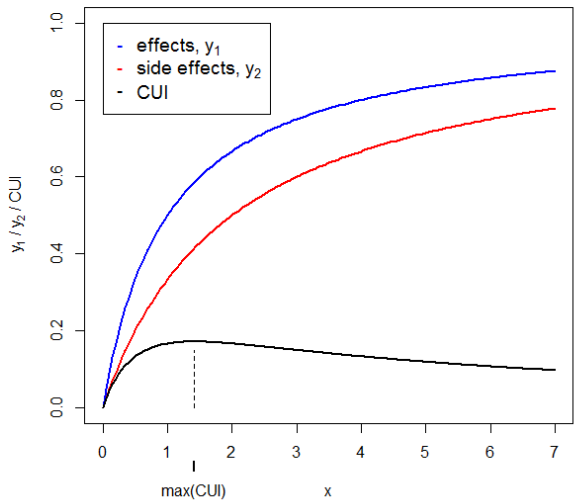

Figure 2.1: The expected effects, side-effects and CUI are shown as functions of dose. Underlying is the bivariate Emax model with parameters $E_{max,1} = E_{max,2} = 1$, $ED_{50,1} = 1$ and $ED_{50,2} = 2$. The weights are assumed to be equal, $v_1 = v_2 = 0.5$.

3. Optimal Design of Experiments

Optimal design theory deals with designing experiments when a statistical model is used to describe the relationship between response variables and experimental variables. Which design is optimal depends on the statistical model, the design space and the objective of the study. When designing a study it is important that the objectives are clearly specified. The optimality criterion, Ψ, can then be chosen in concordance with the objectives. If the aim is to estimate a model parameter, an optimal design will result in an estimate with minimum variance for a given experimental effort. Thus a study that is not optimal will need more experimental effort, i.e. more experimental runs to get an estimate with the same precision. In practice, the experimental efforts is limited and thus in order to save time and money it is crucial to design an experiment in an efficient way. A non-optimal design, compared to an optimal one, will results in a higher number of subjects needed to conduct the experiment and/or a delay until a successful medicine will be available on the market.

When designing an experiment, the researcher has to make several decisions. Among these are the total number of experimental units and the levels of the experimental variables, such as temperature or quantities of a drug. We refer to a design point as a particular level of the experimental variables such as 10 mg of a drug. Optimal design theory deals with choosing the design points and the allocation of experimental units to the different points. The total number of experimental units N is, however, assumed to be fixed. A design, ξ, is denoted by

$$\xi = \left\{ \begin{array}{cccc} x_1 & x_2 & \dots & x_n \\ w_1 & w_2 & \dots & w_n \end{array} \right\}, \quad 0 \leq w_i \leq 1, \quad \text{and} \quad \sum_{i=1}^{n} w_i = 1,$$

where x_i are the design points, n is the number of design points, and w_i are the proportions of the experimental units that are taken at x_i, $i = 1 \dots n$. Finally χ denotes the design space, the set of possible values for the design points.

3.1 Optimality criteria

The choice of optimality criterion, Ψ, depends on the aim of the study. The aim can, for example, be to estimate the parameters in the model, a function of the parameters or a subset of the parameters. The optimality criterion is usually based on some function of the Fisher information matrix. This is because the asymptotic covariance matrix associated with maximum likelihood (ML) estimates can be estimated by the inverse of the observed Fisher information matrix. It is customary to name the different optimality criteria by letters from the alphabet. In Table 3.1 some common optimality criteria are listed.

G-optimality

G-optimality can be used if the objective is to obtain an estimate of the response, $\hat{y}$, over the design region, χ. A design is G-optimal if it minimizes the maximum over χ of the standardized variance

$$d(x,\xi) = N\frac{\text{var}(\hat{y}(x))}{\sigma^2}.$$

Here the criterion to be minimized is $\Psi(\xi;\theta) = \max_{x\in\chi} d(x,\xi)$.

D-Optimality

D-optimality is a common choice if the objective is to estimate the parameters in the model. For a one parameter model the D-optimality criterion to be minimized is $\Psi = \text{var}(\hat{\theta})$. When there are more than one parameter in the model we want to make the inverse of the standardized information matrix, M^{-1}, small in some sense. Several approaches have been suggested, for example to minimize the maximum value of the diagonal or to minimize the trace of the matrix. The D-optimal designs minimize the determinant of M^{-1}, that is

$$\Psi(\xi;\theta) = |M^{-1}(\xi,\theta)|. \tag{3.1}$$

The reason why D-optimality is often used is that D-optimal designs minimize the joint confidence region of the estimated parameters. Note that in practice it is usually more convenient to minimize the function $\Psi(\xi;\theta) = \log(|M^{-1}(\xi,\theta)|)$ which is equivalent to minimizing Ψ in (3.1) because the logarithm is a monotonically increasing function. Let p denote the number of model parameters. Most D-optimal designs for single response models have $p \le n \le p(p+1)/2$ design points. The number of design points, n, for linear polynomial regression models needs to be at least p if all parameters are to be estimated. The upper bound is a result from Caratheodory's theorem which

gives that when the optimality criteria is a function of a single information matrix then the number of design points, n, is less than or equal to $p(p+1)/2$. However, as we will see in this thesis D-optimal designs for multi-response models can have fewer than p design points. Moreover, Wang [33] shows that there exists D-optimal designs for single response nonlinear models with fewer than p design points.

A very important result in optimal design theory is that G- and D-optimal designs are equivalent although the motivation for them looks very different. This important result was observed by Kiefer and Wolfowitz [34].

D_s-Optimality

D_s-optimal designs are appropriate when the objective of a study is to estimate a subset of s of the model parameters. D_s-optimal designs minimize the joint confidence region of the estimated parameters in the subset. Let $\theta = (\theta_1, \theta_2)$ represent a partition of the model parameters, θ, were θ_1 corresponds to the s parameters of interest and θ_2 the $p-s$ nuisance parameters. Moreover let

$$M(\xi) = \begin{bmatrix} M_{11} & M_{12} \\ M_{12} & M_{22} \end{bmatrix}$$

define the corresponding partition of $M(\xi)$. The D_s-optimality criterion involves minimizing

$$\Psi(\xi; \theta_1, \theta_2) = \frac{|M_{22}(\xi)|}{|M(\xi)|}. \tag{3.2}$$

c-Optimality

c-optimal designs are appropriate when the objective of the study is to estimate some differentiable function, $g(\theta)$, of the parameters. If we denote the ML estimator of θ by $\hat{\theta}$, then the criterion to be minimized is the asymptotic variance of $\sqrt{N}(g(\hat{\theta}) - g(\theta))$ which equals

$$\Psi(\xi; \theta) = \nabla g^T(\theta) M^{-1}(\xi, \theta) \nabla g(\theta), \tag{3.3}$$

where $\nabla g(\theta)$ is the gradient of g with respect to the parameters. Caratheodory's theorem gives that $n \leq p(p+1)/2$. However, different from D-optimal designs, c-optimal designs for single response models can have fewer than p design points. In that case the information matrix becomes singular and a more rigorous treatment involving generalized inverses is needed.

Table 3.1: Some common optimality criteria.

criterion	covariance matrix (asymptotic)	optimality criterion, Ψ	aim is to estimate
D	$M^{-1}(\xi,\theta)$	$\log(\lvert M^{-1}(\xi,\theta)\rvert)$	all parameters
D_s	$M^{11}(\xi,\theta)$	$\log(\frac{\lvert M_{22}(\xi,\theta)\rvert}{\lvert M(\xi,\theta)\rvert})$	a subset of the parameters
D_A	$L^T M^{-1}(\xi,\theta)L$	$\log(\lvert L^T M^{-1}(\xi,\theta)L\rvert)$	linear comb. of the param.$(L^T\theta)$
Linear	$L^T M^{-1}(\xi,\theta)L$	$\mathrm{tr}\{L^T M^{-1}(\xi,\theta)L\}$	linear comb. of the param.$(L^T\theta)$
(c-optimal) linear	$c^T M^{-1}(\xi,\theta)c$	$c^T M^{-1}(\xi,\theta)c$	linear function, $c^T\theta$
(c-optimal) non-linear	$\nabla g(\theta)^T M^{-1}(\xi,\theta)\nabla g(\theta)$	$\nabla g(\theta)^T M^{-1}(\xi,\theta)\nabla g(\theta)$	non-linear function, $g(\theta)$

If a study has several, say k, objectives, a weighted average of the chosen optimality criteria $\bar{\Psi} = m_1\Psi_1 + m_2\Psi_2 + \ldots + m_k\Psi_k$, can be used. The weights m_i are positive numbers that sum up to one and represent the importance of the different objectives.

3.2 General Equivalence Theorems

The most important tool for verifying that a design is optimal is the General Equivalence Theorem (GET). GET is a synonym for several equivalence theorems used to demonstrate that designs are optimal. Their form depends on the model, the design space and the criterion function. The first GET was discovered for D-optimality by Kiefer and Wolfowitz, see [34]. Before taking a look at some GET we need the following Lemma.

Lemma 1. *Let $\varphi(x,\xi)$ stand for the Frechét directional derivative of Ψ in the direction ξ_x and let Ψ be a general criterion function to be minimized. A design, ξ, is locally optimal with respect to Ψ if and only if $\varphi(x,\xi) \geq 0\ \forall x \in \chi$. This further implies that $\varphi(x,\xi) = 0$ for $x \in \{x_1,\ldots,x_n\}$.*

Proof. See for example, Pázman [11]. □

Theorem 1. (GET D-optimality). *Suppose ξ is a design such that $M(\xi)^{-1}$ exists. Then ξ is locally D-optimal if and only if,*

$$tr(M(\xi)^{-1}M(\xi_x)) \quad \leq \quad p, \quad \forall \ x \in \chi. \tag{3.4}$$

Further, the equality holds at $x \in \{x_1,\ldots,x_n\}$.

Proof. A design is locally D-optimal if it minimizes $\Psi = \log|M(\xi)^{-1}| = -\log|M(\xi)|$. First note that the Frechét directional derivative can be written

of the form $\varphi(x,\xi) = tr\Big(\frac{\partial\Psi}{\partial M(\xi)}(M(\xi_x) - M(\xi))\Big)$ (see Pázman [11]). Now

$$\frac{\partial\Psi}{\partial M(\xi)} = -\frac{\partial}{\partial M(\xi)}(\log|M(\xi)|) = -(M(\xi)^T)^{-1} = -M(\xi)^{-1}.$$

It follows that

$$\begin{aligned}\varphi(x,\xi) &= tr(-M(\xi)^{-1}(M(\xi_x) - M(\xi))) \\ &= \underbrace{tr(M(\xi)^{-1}M(\xi))}_{p} - tr(M(\xi)^{-1}M(\xi_x)).\end{aligned}$$

Now

$$\varphi(x,\xi) \geq 0 \quad \Leftrightarrow \quad tr(M(\xi)^{-1}M(\xi_x)) \leq p.$$

□

Theorem 2. (GET D_s-optimality). *Suppose ξ is a design such that $M(\xi)^{-1}$ and $M_{22}(\xi)^{-1}$ exists. Then ξ is locally D_s-optimal if and only if,*

$$tr(M(\xi)^{-1}M(\xi_x)) - tr(M_{22}(\xi)^{-1}M_{22}(\xi_x)) \quad \leq \quad s, \quad \forall \ x \in \chi. \tag{3.5}$$

Further, the equality holds at $x \in \{x_1, ..., x_n\}$.

Proof. Let $\Psi_1 := -\log|M(\xi)|$, $\Psi_2 := -\log|M_{22}(\xi)|$ and $\varphi_1(x,\xi)$, $\varphi_2(x,\xi)$ be the Frechét directional derivatives of Ψ_1 and Ψ_2, respectively, in the direction ξ_x. A design is locally D_s-optimal if it minimizes $\Psi = -\log(\frac{|M(\xi)|}{|M_{22}(\xi)|}) = -(\log(|M(\xi)|) - \log(|M_{22}(\xi)|)) = \Psi_1 - \Psi_2$. We see that the Frechét directional derivative of Ψ, $\varphi(x,\xi)$, equals $\varphi_1(x,\xi)$-$\varphi_2(x,\xi)$ and from Theorem 1 we have that

$$\varphi_1(x,\xi) = p - tr(M(\xi)^{-1}M(\xi_x))$$

$$\varphi_2(x,\xi) = (p-s) - tr(M_{22}(\xi)^{-1}M_{22}(\xi_x)).$$

Hence

$$\begin{aligned}\varphi(x,\xi) &= (p - tr(M(\xi)^{-1}M(\xi_x))) - ((p-s) - tr(M_{22}(\xi)^{-1}M_{22}(\xi_x))) \\ &= s - (tr(M(\xi)^{-1}M(\xi_x)) - tr(M_{22}(\xi)^{-1}M_{22}(\xi_x))).\end{aligned}$$

and

$$\varphi(x,\xi) \geq 0 \quad \Leftrightarrow \quad (tr(M(\xi)^{-1}M(\xi_x)) - tr(M_{22}(\xi)^{-1}M_{22}(\xi_x))) \leq s.$$

□

Theorem 3. (GET c-optimality). *Suppose ξ is a design such that $M(\xi)^{-1}$ exists. Then ξ is locally c-optimal with respect to a non-linear function of the model parameters, $g(\theta)$, if and only if,*

$$\nabla g^T M(\xi)^{-1} M(\xi_x) M(\xi)^{-1} \nabla g \;\leq\; \nabla g^T M(\xi)^{-1} \nabla g, \quad \forall\; x \in \chi. \tag{3.6}$$

Further, the equality holds at $x \in \{x_1, ..., x_n\}$.

Proof. The proof is similar to the proof of Theorem 1 and is provided in paper II. □

The GET can be used to verify which designs are optimal and which are not. Searching for an optimal design can however be very challenging. In this thesis two main approaches are used for finding optimal designs. The first approach involves using an informal guess on the number of design points and their weights and then searching numerically for the levels of the design points that minimize Ψ. The other approach involves using a version of the V-algorithm, see Atkinson [10]. The V-algorithm used in this thesis takes in an initial design, ξ, and adds to the design a design point that maximizes the left hand side of (3.4), (3.6) or (3.5), depending on which optimality criterion is of interest. The same weight is given to all design points and the algorithm is repeated a large number of times. The resulting design can have many design points. Design points close to each other are combined and their frequency used to construct weights. This procedure often leads to an optimal design. The GET theorem is always used to check whether the constructed designs are optimal or not. Numerical calculations in this thesis are carried out in Mathcad 15 and in R 3.0.2.

Finding closed form expressions for optimal designs is usually more challenging than finding optimal designs numerically. Closed form D-optimal designs for the Emax model are shown in Table 3.2. For references see; Burman, Miller and Wong [35] for the one parameter Emax model, Dette, Kiss and Wong [16] for the two parameter Emax model and Dette, Kiss and Bevanda [14] for the three parameter Emax model.

Table 3.2: D-optimal designs for the Emax model.

Model	χ	Design
$f(x) = \frac{x}{x+ED_{50}}$	$[0,\infty[$	$\xi^* = \left\{ \begin{array}{c} ED_{50} \\ 1 \end{array} \right\}$
$f(x) = E_{max}\frac{x}{x+ED_{50}}$	$[a,b]$	$\xi^* = \left\{ \begin{array}{cc} \max(a, s_b ED_{50}) & b \\ 1/2 & 1/2 \end{array} \right\}$
$f(x) = E_0 + E_{max}\frac{x}{x+ED_{50}}$	$[a,b]$	$\xi^* = \left\{ \begin{array}{ccc} a & x^* & b \\ 1/3 & 1/3 & 1/3 \end{array} \right\}$

Here $x^* := \frac{b(a+ED_{50})+a(b+ED_{50})}{(a+ED_{50})+(b+ED_{50})}$, $s_b := \frac{b/ED_{50}}{2+(b/ED_{50})}$ and $\lim_{b\to\infty} s_b = 1$.

4. Summary of papers

4.1 Optimal designs for finding the dose that maximizes a Clinical Utility Index (Paper I)

In paper I, we consider the problem of optimally designing dose response studies, aimed at estimating the dose that maximizes the Clinical Utiltiy Index (CUI). We directly model the CUI for a given dose of a drug. The expected CUI consists of a weighted average of an efficacy variable and a safety variable which are represented with three and two parameter Emax models, respectively. In other words, we use Emax models for both an efficacy and a safety profile but combine them into a single metric, the CUI, before data is fitted.

We derive some locally c-optimal designs for estimating the dose that maximizes the CUI. The resulting designs have four design points where two are at the boundary of the design space. Most of the weight is, however, assigned to the other two design points that are asymmetrically located around the dose that gives the highest CUI. Some locally c-optimal designs for a simplified CUI model are also derived. In the simplified CUI model, single parameter Emax models are used to assess both efficacy and safety. The c-optimal designs for the simplified CUI have two equally weighted design points which, on a logarithmic scale, are symmetrically located around the dose that maximizes the CUI.

Efficiency plots are used to study how sensitive the designs are to misspecification of prior guesses for the parameter values. We conclude that the efficiencies of the c-optimal designs are good when the true SD_{50} and E_{max} parameters are equal to or larger than expected. This suggests that one might consider using a prior guess that is somewhat lower than the informed guess.

Finally, simulation is used to show that the c-optimal designs are appropriate for small sample sizes and perform well in comparison to classical dose finding studies.

4.2 Optimal design problems for the bivariate Emax model (Paper II)

The aim of paper II is to derive locally c-optimal designs for the bivariate Emax model with error terms following a bivariate normal distribution. The bivariate Emax model is used to describe how an efficacy and a safety variable change with dose of a drug. As in paper I the interest is on estimating the dose that maximizes the CUI. While the CUI in paper I is a model consisting of a mean profile and an error term, the CUI in paper II is merely a function consisting of a weighted average of expected efficacy and safety.

In paper II, we provide a GET for multi-response c-optimality together with a proof. This theorem is a special case of the GET for linear optimality which has been proved previously, see Fedorov [12]. The locally c-optimal designs that we derive for the bivariate Emax model are two or three point designs. We also derive designs for a simplified version of the bivariate Emax model where each profile consists of a single parameter Emax model. For the simplified model the derived c-optimal designs are one or two point designs.

An interesting question is how the optimal designs depend on the model and covariance parameters. First, we provide a theorem that shows that, without loss of generality, some of the parameters can be set equal to one. The remaining parameters are then varied and different c-optimal designs are derived. The results indicate that when the correlation, ρ, and the ratios σ_2^2/σ_1^2 and SD_{50}/ED_{50} are sufficiently small one less design point is needed as compared to when ρ and the ratios are large. It is interesting that a model with large negative ρ results in a design with one less design point than a model with large positive ρ. In order to investigate further how important information on ρ is when deriving an optimal design, a simulation study is carried out. The simulation indicates that the locally c-optimal designs for the bivariate Emax model are not sensitive to misspecification of ρ.

A shortened version of paper II is published in mODa 10, see [1]. The main difference between the papers is that in the mODa version of the paper some results for the simplified model are excluded and the section concerning the simulation study is also excluded due to space limitation.

4.3 Simultaneous estimation of parameters in the bivariate Emax model (Paper III)

Results from paper II show that the correlation ρ plays a role for the optimal design for the bivariate Emax model. However, when working with simulated data in paper II, the two profiles of the bivariate Emax model are fitted sepa-

rately without using information about ρ. The aim of paper III is to investigate how information about the correlation can be used when fitting multi-response, nonlinear models and how important it is to use information about the correlation.

In paper III, we theoretically work out a system estimation approach for simultaneous estimation and inference of parameters in multi-response models. In short, the approach involves iteratively using ML estimates of Σ to derive ML estimates for the model parameters which in turn are used to derive new ML estimates of Σ. This procedure is iterated until the parameter estimates are stable. We note that other authors have also considered the problem of estimating parameters in multi-response models, see for example Bates and Watts [17] and Marshall [18].

By means of simulation we investigate how much can be gained by using the system estimation approach as compared to an equation-by-equation approach. This is done by using both approaches for fitting the bivariate Emax model to simulated datasets. We investigate in total 24 simulation settings where the parameters ED_{50} and ρ are varied while other parameters are fixed. Each simulation setting is repeated with new simulated datasets until results from $R = 10000$ convergent replications are obtained.

The main results from the simulation study are that when $\rho \neq 0$ system estimation increases the precision of some but not necessarily all parameter estimates in the bivariate Emax model. We reason that system estimation uses the correlation information to increase the precision for parameters that are difficult to estimate, sometimes at the expense of other parameters. The overall gain in precision for the parameters in the bivariate Emax model is, however, positive and increases with $|\rho|$. Further, we conclude that the study design is of central importance for the efficiency gain. When study designs are not efficient, system estimation can substantially increase the precision of parameter estimates.

4.4 Optimal designs for a multi-response Emax model and effcient parameter estimation (Paper IV)

The aim of paper IV is to combine ideas from papers I-III and to apply theoretical results to real dose response data. In papers I and II we consider optimal designs that are efficient for obtaining precise estimates. In paper III we see that choosing a good estimation approach is also important in order to obtain precise estimates. Here, in paper IV, we work with real data and consider how to obtain precise parameter estimates both by choosing a good estimation approach and by using an optimal study design.

The data comes from a phase II clinical study. The objective of the study was to evaluate a new compound as add-on treatment for patients with type 2 diabetes. We work with four important response variables from the study and fit a multi-response Emax model to the data.

We compare equation-by-equation estimation and system estimation by first fitting uni-response Emax models separately to the profiles and then fitting a multi-response Emax model to the profiles. The system estimation approach results in smaller standard errors for the parameters in two out of four profiles. We reason that, overall, system estimation is beneficial and is recommended unless possibly when assessment of different profiles are not of equal importance. Moreover we note that system estimation should be used with caution if there are uncertainties concerning the chosen model for one or more of the profiles.

Optimal designs for a multi-response Emax model depend on prior guesses for the parameter values. We use the system estimation parameter estimates as a prior guess and provide optimal designs for the multi-response Emax model. We derive both a D-optimal design that minimizes the confidence region for the estimated parameters and a D_s-optimal design that minimizes the confidence region for a subset of the estimated parameters. We show that the designs are not very sensitive to misspecification of prior values. Moreover we show that the design that was used in the diabetes dose response study is very inefficient for estimating parameters in the multi-response Emax model, as compared to D- and D_s-optimal designs.

5. Summary and further research

5.1 Summary

This thesis centers around optimal designs for Emax models and multi response Emax models. In paper I two separate Emax models are used to model efficacy and safety. In papers II and III the focus is on the bivariate Emax model and in paper IV on a multi response Emax model with four responses.

In papers I and II we derive c-optimal designs that are efficient for estimating the dose that maximizes the CUI. The main difference between papers I and II is that in paper I the CUI is a model fitted directly to the data while in paper II we work with the bivariate Emax model and the CUI is merely a function of the expected efficacy and safety. Moreover we include a placebo effect for the efficacy profile in paper I but not in paper II. In both papers we also derive locally c-optimal designs where both profiles consist of a simplified Emax model including only one parameter. By comparing the designs from paper I and II that are based on one parameter Emax models and on the same prior values we see that the designs differ remarkably. Some of the designs in paper II are one point designs while the corresponding designs in paper I are two point designs. This is because some information is lost when the approach in paper I is used and results from the two response variables are combined into a single observation. Moreover, when both approaches lead to two equally weighted design points, in paper II these points are close to each other while in paper I they are further away from each other.

Comparison of system estimation and equation-by-equation estimation is carried out in papers III and IV. In paper III an extensive simulation study is carried out in order to compare how well these two estimation approaches perform when fitting the bivariate Emax model. In paper IV, the performances of the two approaches are compared by fitting an Emax model with four responses to real dose response data. The main results from these papers are that system estimation can substantially increase the precision of parameter estimates, especially when the correlation between response profiles is strong and when the study has not been designed in an efficient way. As with all estimation approaches, system estimation should be used with caution if there are uncertainties about the chosen model for one or more of the response profiles.

The results further show that system estimation sometimes increases the precision of parameters that are difficult to estimate, while reducing the precision of other parameters. Thus in case parameters in different profiles are not of equal importance an equation-by-equation estimation might be preferable. In paper IV, besides comparing the two estimation approaches, some locally D- and D_s-optimal designs for a multi-response Emax model with four responses are derived. The system estimation estimates that were derived from the real dose response data are used as prior values for the designs.

The locally optimal designs derived in this thesis depend upon prior values for the parameters. In order to study how sensitive our designs are we assume that prior values have been misspecified and calculate the efficiency of our designs as compared to an optimal design based on prior values assumed to be correct. This is an important part of both paper I and IV.

5.2 Suggestions for further research

As noted earlier, many have studied optimal designs for a single-response Emax model, but this thesis is among the first to consider optimal designs for multi-response Emax models. A primary focus in the thesis is to derive c-optimal designs for estimating the dose that maximizes the CUI. In this thesis we have defined the CUI as a weighted average of efficacy and safety. For some drugs it might, however, be appropriate to define CUI in some other way such as the ratio between efficacy and safety. The methodology used in papers I or II could be used to derive c-optimal designs based on CUI functions defined in different ways. In paper IV we derived some locally D- and D_s-optimal designs for a four dimensional Emax model. It would be very interesting to try to derive closed form D- and D_s-optimal designs for multi-response Emax models. The designs will depend upon, but probably not be very sensitive to, changes in the correlation parameters. A suggestion is to initially assume zero correlation before looking for closed form expressions.

Finally we note that there are many things that remain to be done in order to compare system estimation and equation-by-equation estimation. We used extensive simulations to compare these two approaches when fitting the bivariate Emax model. The results are however subtle and can not be generalized to other models. A suggestion for further work is thus to conduct simulation studies for other models. In our simulation study a classical design with equal allocation and equally spaced dose groups was used. It would be interesting to use an optimal or a close to optimal design and investigate the impact the design has on the efficiency gain. Moreover, an optimal design is likely to lead to fewer nonconvergent scenarios as compared to the classical design.

Swedish summary

I denna avhandling studeras konstruktion av optimala designer samt skattningsmetoder för multi-respons Emax modeller. Dessa modeller förklarar sambandet mellan dosen av ett läkemedel och två eller flera effekt- och/eller bieffektvariabler. Att använda optimala designer och bra skattningsmetoder är viktigt eftersom man vill få parameterskattningar med så stor precision som möjligt.

Vi konstruerar optimala designer som är effektiva för att skatta modellparametrar i multi-respons Emax modeller. Vi konstruerar också optimala designer för att skatta en delmängd av parametrarna respektive en funktion av parametrarna. Funktionen av intresse är en skattning av en dos som kan rekommenderas för en grupp av patienter, dvs. den dos som maximerar The Clinical Utility Index (CUI), vilken mäter nyttan av en dos genom att ta hänsyn till både effekter och bieffekter.

De designer som konstrueras beror av sanna värden på modellparametrarna. När dos-respons studier planeras har man ofta en del information från tidigare studier. Denna information kan användas för att gissa värdet på parametrarna. En viktig del i avhandlingen är att studera hur känsliga optimala designerna är för fel val av parametervärden.

Parametrarna i multi-respons Emax modellerna kan skattas med Maximum Likelihhod (ML) metoden på två olika sätt. Ett sätt är att skatta varje responsprofil seperat med hjälp av ML metoden. Ett annat sätt är att skatta parametrarna i alla profiler samtidigt genom att använda information om hur de olika responsprofilerna korrelerar med varandra. Vi använder både simulering och data från en klinisk studie för att jämföra precisionen hos skattningar från de två metoderna. Vi kommer fram till den slutsatsen att en simultanskattning ger betydligt bättre skattningar, speciellt när responsprofilerna korrlerar starkt med varandra och när designen som används inte är optimal. Vi konstanterar också att simultan-skattning ger ibland bättre skattningar för de parametrar som är svåra att skatta på bekostnad av parametrar som är lätta att skatta.

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