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Optimal designs for some selected nonlinear models

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ABSTRACT

Some design aspects related to three complex nonlinear models are studied in this paper. For Klimpel's flotation recovery model, it is proved that regardless of model parameter and optimality criterion, any optimal design can be based on two design points and the right boundary is always a design point. For this model, an analytical solution for a D-optimal design is derived. For the 2-parameter chemical kinetics model, it is found that the locally D-optimal design is a saturated design. Under a certain situation, any optimal design under this model can be based on two design points. For the $2n$-parameter compartment model, compared to the upper bound by Carathéodory's theorem, the upper bound of the maximal support size is significantly reduced by the analysis of related Tchebycheff systems. Some numerically calculated A-optimal designs for both Klimpel's flotation recovery model and 2-parameter chemical kinetic model are presented. For each of the three models discussed, the D-efficiency when the parameter misspecification happens is investigated. Based on two real examples from the mining industry, it is demonstrated how the estimation precision can be improved if optimal designs would be adopted. A simulation study is conducted to investigate the efficiencies of adaptive designs.

1. Introduction

Optimal designs based on nonlinear models have wide and important applications in many areas of science. A good example of the application is the optimal design based on PK/PD models which are widely used in pharmaceutical industries for the examination of absorption, distribution, metabolism, elimination, efficacy and toxicity parameters in drug developments, see Gieschke and Steimer (2000) and Meibohm and Derendorf (2002).

We study and explore optimal designs for three complex nonlinear models. These are the 2-parameter chemical kinetic model, the $2n$-parameter compartment model and the 2-parameter Klimpel's flotation recovery model. These three models have been shown to have extensive applications in real life situations (Godfrey, 1983; Jacquez, 1985; Parekh and Miller, 1999; Saleh, 2010; Yuan et al., 1996).

We concentrate on the nonlinear model $y=\eta(x,\boldsymbol{\theta})+\varepsilon$, where $\boldsymbol{\theta}=(\theta_1,\theta_2,\ldots,\theta_k)^T$ is a vector of k unknown parameters and x is the explanatory variable defined on a design space χ in $\mathbb{R}$. The error ε is postulated to be distributed as $N(0,\sigma^2)$ and without loss of generality we let $\sigma=1$. Further, we assume that all observations are independent.

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Typically, the optimal nonlinear design studies are under approximate theory, i.e., instead of exact sample sizes for design points, design weights are used. Let ξ be any n-point approximate design,

$$\boldsymbol{\xi}=\begin{pmatrix} t_1 & t_2 & \dots t_n \\ \omega_1 & \omega_2 & \dots \omega_n \end{pmatrix}.$$

Here $0<\omega_i<1$ represents the proportion of the number of points studied at t_i with $\sum_{i=1}^{n}\omega_i=1$. The Fisher information matrix for $y=\eta(t,\boldsymbol{\theta})+\varepsilon$ can be written as

$$I_\xi=\sum_{i=1}^{n}\omega_i\left(\frac{\partial\eta(t,\boldsymbol{\theta})}{\partial\boldsymbol{\theta}}\right)\left(\frac{\partial\eta(t,\boldsymbol{\theta})}{\partial\boldsymbol{\theta}}\right)^T. \tag{1.1}$$

How to compare two designs? There are variety of optimality criteria. Two popular optimality criteria are D-optimality and A-optimality, which are to maximize $|I_\xi|$ and minimize $\mathrm{Tr}(I_\xi^{-1})$ over all possible designs, respectively. A D-optimal design minimizes the volume of an asymptotic confidence ellipsoid for θ, and an A-optimal design minimizes the average of the asymptotic variances for the estimators of the individual parameters.

2. Preliminaries

In this paper, we shall use and deal with Extended Tchebycheff systems and Extended Complete Tchebysheff systems. The Tchebycheff systems were first introduced by the Russian mathematicians Chebyshev (1859) and Bernshtein (1937). In Karlin and Studden (1966), the theory of the Tchebycheff systems and its applicability in optimal design of experiments theory is introduced and studied.

Let $\{u_0,u_1,\dots,u_n\}$ be $n+1$ continuous real-valued functions on $[a,b]$. $\{u\}_{k=0}^{n}=\{u_0,u_1,\dots,u_n\}$ is called a Tchebycheff system (T-system) if the following determinant is strictly positive whenever $a\le t_0<t_1<\dots<t_n\le b$

$$U\begin{pmatrix} 0, & 1, & \dots, & n \\ t_0, & t_1, & \dots, & t_n \end{pmatrix}=\begin{vmatrix} u_0(t_0) & u_0(t_1) & \cdots & u_0(t_n) \\ u_1(t_0) & u_1(t_1) & \cdots & u_1(t_n) \\ \vdots & \vdots & \vdots & \vdots \\ u_n(t_0) & u_n(t_1) & \cdots & u_n(t_n) \end{vmatrix}>0.$$

$\{u\}_{k=0}^{n}$ is called a Complete Tchebycheff system (CT-system) if $\{u\}_{k=0}^{m}$ is a T-system on $[a,b]$ for each $m=0,1,\dots,n$. In the sequel, we shall deal with Extended Tchebycheff system and Extended Complete Tchebysheff system, which are defined below:

(i) $\{u\}_{k=0}^{n}$ on $[a,b]$ is called an Extended Tchebycheff system (ET-system) of order p, provided $u_i\in C^{p-1}[a,b]$, $i=0,1,\dots,n$ and

$$U^*\begin{pmatrix} 0, & 1, & \dots, & n \\ t_0, & t_1, & \dots, & t_n \end{pmatrix}>0$$

for all choices $a\le t_0\le t_1\le\dots\le t_n\le b$, where equality occurs in groups of at most p consecutive t_i values. Here,

$$U^*\begin{pmatrix} 0, & 1, & \dots, & n \\ t_0, & t_1, & \dots, & t_n \end{pmatrix}$$

has the same definition as

$$U\begin{pmatrix} 0, & 1, & \dots, & n \\ t_0, & t_1, & \dots, & t_n \end{pmatrix}$$

except that, for each set of equality t_i, we replace successive columns by their successive derivatives. For example, suppose $a\le t_0=t_1=\dots=t_q<t_{q+1}<\dots<t_{n-1}=t_n\le b$ then

$$U^*\begin{pmatrix} 0, & 1, & \dots, & n \\ t_0, & t_1, & \dots, & t_n \end{pmatrix}=\begin{vmatrix} u_0(t_0) & u_0^{(1)}(t_0) & \cdots & u_0^{(q)}(t_0) & u_0(t_{q+1}) & \cdots & u_0(t_{n-1}) & u_0^{(1)}(t_{n-1}) \\ u_1(t_0) & u_1^{(1)}(t_0) & \cdots & u_1^{(q)}(t_0) & u_1(t_{q+1}) & \cdots & u_1(t_{n-1}) & u_1^{(1)}(t_{n-1}) \\ \vdots & \vdots & \cdots & \vdots & \vdots & \cdots & \vdots & \vdots \\ u_n(t_0) & u_n^{(1)}(t_0) & \cdots & u_n^{(q)}(t_0) & u_n(t_{q+1}) & \cdots & u_n(t_{n-1}) & u_n^{(1)}(t_{n-1}) \end{vmatrix}.$$

In the above, $u_k^{(j)}(t)$ denotes the jth order derivative of u_k.

(ii) $\{u\}_{k=0}^{n}$ is called an Extended Complete Tchebysheff system (ECT-system) if $\{u\}_{k=0}^{m}$ is an ET-system on $[a,b]$ for each $m=0,1,\dots,n$.

The following results are known and we skip the proofs.

(a) $\{u\}_{k=0}^{n}$ on $[a,b]$ is a Tchebysheff system if and only if every non-trivial linear combination $g(t)=\sum_{i=0}^{n}c_iu_i(t)$ has at most n zeros, where $(c_0,c_1,\dots,c_n)\ne(0,0,\dots,0)$.