

## STANDARDIZED MAXIMIN $E$ -OPTIMAL DESIGNS FOR THE MICHAELIS-MENTEN MODEL

Holger Dette<sup>1</sup>, Viatcheslav B. Melas<sup>2</sup> and Andrey Pepelyshev<sup>2</sup>

<sup>1</sup>*Ruhr-Universität Bochum and* <sup>2</sup>*St. Petersburg State University*

*Abstract:* In the Michaelis-Menten model we determine efficient designs by maximizing a minimum of standardized  $E$ -efficiencies. It is shown in many cases that optimal designs are supported at only two points and that the support points and corresponding weights can be characterized explicitly. Moreover, a numerical study indicates that two point designs are usually very efficient, even if they are not optimal. Some practical recommendations for the design of experiments in the Michaelis-Menten model are given.

*Key words and phrases:* Chebyshev system,  $E$ -optimal designs, Michaelis-Menten model, minimax-optimality, standardized optimal designs.

### 1. Introduction

The Michaelis-Menten model

$$E[Y | t] = \frac{at}{t + b}, \quad t \in [0, t_0], \quad (1.1)$$

is widely used to describe physical and biological phenomena (see Cressie and Keightley (1979), Johansen (1984), Beverton and Holt (1957), Cornish-Browden (1979), Hay, Mezmarich, DiGiacomo, Hirst and Zerbe (1988) among many others) and the problem of designing experiments for this model has found considerable attention in the literature (see Duggleby (1979), Dunn (1988), Rasch (1990), Boer, Rasch and Hendrix (2000) or Dette and Wong (1999)). An approximate design  $\xi$  is a probability measure with finite support on the interval  $[0, t_0]$  (see Kiefer (1974), Silvey (1980) or Pukelsheim (1993)). Here the support points  $t_1, \dots, t_k$  represent the locations where observations are taken, and the masses  $w_1, \dots, w_k$  give the proportion of the total observations to be taken at the particular points. If  $n$  independent observations with constant variance  $\sigma^2 > 0$  have been obtained from the design  $\xi$  (possibly with an appropriate rounding of the quantities  $nw_j$ ,  $j = 1, \dots, k$ , see e.g., Pukelsheim and Rieder (1992)), then under the assumption of normality, the covariance matrix of the maximum likelihood estimate of the parameters  $(a, b)^T$  is approximately equal to the matrix

$\sigma^2 n^{-1} M^{-1}(\xi, a, b)$ , where

$$M(\xi, a, b) = \int_0^{t_0} \frac{t^2}{(b+t)^2} \begin{pmatrix} 1 & -\frac{a}{b+t} \\ -\frac{a}{b+t} & \frac{a^2}{(b+t)^2} \end{pmatrix} d\xi(t) \quad (1.2)$$

denotes the information matrix of the design  $\xi$ . Note that this matrix depends on the unknown parameters and, following Chernoff (1953), we call a design locally  $\phi$ -optimal if it maximizes a concave function of the information matrix (1.2). Locally  $D$ -optimal designs ( $\phi(M) = \log |M|$ , where  $|\cdot|$  denotes the determinant) have been determined by Rasch (1990) and have equal weights at the points  $[b/(2b+1)]t_0$  and  $t_0$ . Locally  $E$ -optimal designs ( $\phi(M) = \lambda_{\min}(M)$ , where  $\lambda_{\min}$  denotes the minimal eigenvalue) have been found in Dette and Wong (1999) and have weights  $1-w$  and  $w$  at the points  $t_0$  and  $(\sqrt{2}-1)t_0 b \cdot \{(2-\sqrt{2})t_0 + b\}^{-1}$ , respectively, where the weight  $w$  is given by

$$w = \frac{\sqrt{2}a^2/b\{b\sqrt{2} - (4-3\sqrt{2})t_0\}}{2(t_0+b)^2 + a^2/b^2\{b\sqrt{2} - (4-3\sqrt{2})t_0\}^2}. \quad (1.3)$$

These designs have been criticized for several reasons. On the one hand the designs depend sensitively on the unknown parameters and are in this sense not robust. On the other hand, even if prior knowledge about the parameters is available, it was pointed out in Dette (1997a,b) that, for specific parameter constellations,  $E$ -optimal designs can perform particularly bad. For example if  $a$  is small compared to  $b$ , the weight in (1.3) is close to 0 and consequently the information matrix of the corresponding design is nearly singular. As a numerical example consider the situation discussed in Cressie and Keightley (1981) where  $t_0 = 2000$ , the parameter estimates are  $\hat{a} = 43.95$  and  $\hat{b} = 236.53$ , and a locally  $E$ -optimal design for the parameter  $(a, b) = (44, 237)$  would take 99.91% at the point  $t_0$ . In this case the  $E$ -optimal design is inefficient for estimating both parameters (note that this problem does not appear for the  $D$ -optimality criterion).

Some effort has been undertaken to construct robust designs with respect to the  $D$ -criterion (see Song and Wong (1998) or Dette and Biedermann (2002)) but to our knowledge, robust designs based on the  $E$ -optimality criterion are not available in the literature. It is the purpose of the present paper to construct some. For this, we use a maximin approach introduced by Müller (1995) (see also Dette (1997a)). A design  $\xi^*$  is called standardized maximin  $\phi$ -optimal if it maximizes the function

$$\psi(\xi) = \min_{a \in A, b \in B} \frac{\phi(M(\xi, a, b))}{\max_{\eta} \phi(M(\eta, a, b))}, \quad (1.4)$$

where  $\phi$  is a concave function and the minimum is taken over certain subsets  $A$  and  $B$  of the parameter space specified by the experimenter. In many applications such a specification is available, see for example Cressie and Keightley (1981, p.237), where a specific range for the dissociation constant  $b$  for the receptor-estradiol interaction is given. Note that the criterion  $\psi$  in (1.4) is a minimum of  $\phi$ -efficiencies taken over a certain range of the parameters and is in this sense very intuitive. We will not use the function  $\phi(M) = \lambda_{\min}(M)$  corresponding to the  $E$ -optimality criterion directly (because of its deficiencies mentioned in the previous paragraph), but rather a modified version introduced in Dette (1997b). This uses a scaling of the elements in the information matrix, similar to the transition from the covariance to the correlation matrix. The new criterion is carefully defined in a general context in Section 2, which also gives some preliminary results and an equivalence theorem for the standardized maximin optimality criterion. In Section 3 we determine optimal designs for the Michaelis-Menten model and prove that, for a sufficiently small set  $B$  for the parameter  $b$ , the standardized maximin  $E$ -optimal design is always supported at two points. To our knowledge a property of this type has been found in the context of Bayesian or maximin optimality criteria (see Chaloner and Larntz (1989) or Haines (1995)) but has never been proved rigorously in a non-trivial situation such as the Michaelis-Menten model. Numerical results are presented in Section 4, which also gives some practical recommendations, while Section 5 contains an appendix with a technical result used for the proofs in Sections 2 and 3.

## 2. The Standardized Maximin $E$ -optimality Criterion

Consider the regression model

$$E[Y | t] = \sum_{i=1}^k a_i \varphi(t, b_i); \quad t \in I, \quad (2.1)$$

where  $\varphi(t, b)$  is a given function,  $I$  is an interval and  $a = (a_1, \dots, a_k)^T$ ,  $b = (b_1, \dots, b_k)^T$  denote the vectors of the unknown parameters. Note that the Michaelis-Menten model discussed in the introduction is obtained by the choice  $k = 1$ ,  $I = [0, t_0]$  and  $\varphi(t, b_1) = t/(t + b_1)$ . The Fisher information matrix in the model (2.1) is given by

$$M(\xi, a, b) = D_a \int_I f(t, b) f^T(t, b) d\xi(t) D_a, \quad (2.2)$$

$$f(t, b) = (f_1(t, b), \dots, f_{2k}(t, b))^T = (\varphi(t, b_1), \varphi'(t, b_1), \dots, \varphi(t, b_k), \varphi'(t, b_k))^T \in \mathbb{R}^{2k}, \quad (2.3)$$

where  $f$  is the vector of regression functions. Derivatives of  $\varphi$  are taken with respect to its second argument, and the matrix  $D_a \in \mathbb{R}^{2k \times 2k}$  is defined by

$$D_a = \begin{pmatrix} 1 & 0 & 0 & \dots & 0 & 0 \\ 0 & a & 0 & \dots & 0 & 0 \\ 0 & 0 & 1 & \dots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & 1 & 0 \\ 0 & 0 & 0 & \dots & 0 & a \end{pmatrix}. \quad (2.4)$$

Detle (1997b) points out several drawbacks of designs maximizing  $\lambda_{\min}(M(\xi, a, b))$ . In particular, in many regression models, these designs become inefficient for estimating the complete vector of parameters, while a standardized version of the  $E$ -optimality criterion avoids these problems. We use this criterion for the construction of robust designs. To be precise let  $e_j = (0, \dots, 0, 1, 0, \dots, 0)^T$  denote the  $j$ th unit vector and  $\xi_j^*$  denote the locally  $e_j$ -optimal design minimizing the expression  $e_j^T M^{-}(\xi, a, b) e_j$ ,  $j = 1, \dots, 2k$ , where  $M^{-}$  denotes a generalized inverse of the matrix  $M$ . We assume that the  $j$ th parameter in (2.1) is estimable by the design  $\xi$ , that is  $e_j \in \text{range}(M(\xi, a, b))$  for all  $a, b$ . A standardized  $E$ -optimality criterion is defined as follows (see Dette (1997a,b)). Let

$$K_{a,b} = \text{diag}\left\{(e_1^T M^{-}(\xi_1^*, a, b) e_1)^{-1/2}, \dots, (e_{2k}^T M^{-}(\xi_{2k}^*, a, b) e_{2k})^{-1/2}\right\} \quad (2.5)$$

denote a diagonal matrix with  $j$ th entry proportional to the inverse square root of the best ‘‘variance’’ obtainable by the choice of an experimental design for estimating the  $j$ th coefficient in (2.1), and define the matrix

$$C(\xi, b) = (K_{a,b}^T M^{-}(\xi, a, b) K_{a,b})^{-1}. \quad (2.6)$$

Following Dette (1997a), a design maximizing the function

$$\lambda_{\min}(C(\xi, b)) = \lambda_{\min}((K_{a,b}^T M^{-}(\xi, a, b) K_{a,b})^{-1}) = \lambda_{\min}((K_{1,b}^T M^{-}(\xi, 1, b) K_{1,b})^{-1}) \quad (2.7)$$

is termed locally standardized  $E$ -optimal (in the last equality we use the notation  $1 = (1, \dots, 1)^T \in \mathbb{R}^k$ ). Recalling the definition of the matrices in (2.2), (2.3), (2.4) and Theorem 3.2 in Dette (1997b), it follows that the matrix in (2.6) does not depend on the linear parameters  $a_1, \dots, a_k$  of (2.1), which justifies the last equality and our notation  $C(\xi, b)$ .

**Definition 2.1.** A design  $\xi^*$  is called standardized maximin  $E$ -optimal if it maximizes the function

$$\min_{b \in B} \frac{\lambda_{\min}(C(\xi, b))}{\max_{\eta} \lambda_{\min}(C(\eta, b))}, \quad (2.8)$$

where the matrix  $C(\xi, b)$  is defined in (2.6) and  $B \subset \mathbb{R}^k$  is a given set.

Throughout this paper we assume that the functions  $f_1, \dots, f_{2k}$  defined in (2.3) generate a Chebyshev system on the interval  $I$  (for any  $b$ ). A set of functions  $f_1, \dots, f_m : I \rightarrow \mathbb{R}$  is called a weak Chebyshev system (on the interval  $I$ ) if there exists an  $\varepsilon \in \{-1, 1\}$  such that

$$\varepsilon \cdot \begin{vmatrix} f_1(x_1) & \dots & f_1(x_m) \\ \vdots & \ddots & \vdots \\ f_m(x_1) & \dots & f_m(x_m) \end{vmatrix} \geq 0 \quad (2.9)$$

for all  $x_1, \dots, x_m \in I$  with  $x_1 < x_2 < \dots < x_m$ . If the inequality in (2.9) is strict, then  $\{f_1, \dots, f_m\}$  is called Chebyshev system. It is well known (see Karlin and Studden (1966, Theorem II 10.2) that if  $\{f_1, \dots, f_m\}$  is a weak Chebyshev system, then there exists a unique function

$$\sum_{i=1}^m c_i^* f_i(t) = c^{*T} f(t), \quad (2.10)$$

with the following properties

- (i)  $|c^{*T} f(t)| \leq 1 \quad \forall t \in I$
  - (ii) there exist  $m$  points  $s_1 < \dots < s_m$  such that  $c^{*T} f(s_i) = (-1)^{i-1}$
- $i = 1, \dots, m.$

The function  $c^{*T} f(t)$  is called a Chebyshev polynomial and gives the best approximation of the function  $f_0(t) \equiv 0$  by normalized linear combinations of the system  $f_1, \dots, f_m$  with respect to the sup-norm. The points  $s_1, \dots, s_m$  are called Chebyshev points and need not be unique. They are unique if  $1 \in \text{span}\{f_1, \dots, f_m\}$  and  $I$  is a bounded and closed interval, where in this case  $s_1 = \min_{x \in I} x$ ,  $s_m = \max_{x \in I} x$ . It is well known (see Studden (1968), Pukelsheim and Studden (1993) or Imhof and Studden (2001) among others) that in many cases the  $E$ - and  $c$ -optimal designs are supported at the Chebyshev points. Our first lemma shows that this is also the case for the locally  $e_j$ -optimal designs and the locally standardized  $E$ -optimal design which maximizes the function defined by (2.7).

**Lemma 2.2.** *Assume that (for fixed  $b$ ) the functions  $f_1(\cdot, b), \dots, f_{2k}(\cdot, b)$  in (2.3) generate a Chebyshev system on the interval  $I$  with Chebyshev polynomial  $f^T(t, b)c^*$  and Chebyshev points  $t_1^* < t_2^* < \dots < t_{2k}^*$ . If any subsystem of  $2k - 1$  of the functions  $f_1(\cdot, b), \dots, f_{2k}(\cdot, b)$  is a weak Chebyshev system on the interval  $I$ , then the following assertions are true:*

- (a) For every  $j = 1, \dots, 2k$  the design  $\xi_j^* = \begin{pmatrix} t_1^* & \dots & t_{2k}^* \\ w_{1,j} & \dots & w_{2k,j} \end{pmatrix}$  is  $e_j$ -optimal for the model (2.1), where the weights are defined by  $w_{i,j} = [(-1)^i e_i^T F^{-1} e_j] / [\sum_{\ell=1}^{2k} (-1)^\ell e_\ell^T F^{-1} e_j]$ ,  $i = 1, \dots, 2k$  and the matrix  $F$  is given by  $F = (f_i(t_j^*, b))_{i,j=1}^{2k}$ . Moreover,  $e_j^T M^{-1}(\xi_j^*, 1, b) e_j = (c_j^*)^2$ , where  $c_j^*$  is the  $j$ th coefficient of the Chebyshev polynomial defined by (2.10).
- (b) The design  $\xi_E^* = [1/(2k)] \sum_{\ell=1}^{2k} \xi_\ell^*$  is locally standardized  $E$ -optimal in the model (2.1) and  $\lambda_{\min}(C(\xi_E^*, b)) = 1/(2k)$ .

**Proof.** Note that the optimal designs do not depend on the parameters  $a_1, \dots, a_k$  and we put  $a_j = 1$ ,  $j = 1, \dots, k$  without loss of generality. For a proof of (a), consider a fixed  $j \in \{1, \dots, 2k\}$  and let  $h_j^{-2} = e_j^T M^{-1}(\xi_j^*, 1, b) e_j = (\sum_{\ell=1}^{2k} (-1)^\ell e_\ell^T F^{-1} e_j)^2$ . Then it is easy to see that  $JFw_j = h_j e_j$ , where  $w_j = (w_{1,j}, \dots, w_{2k,j})^T$  and the matrix  $J$  is defined by  $J = \text{diag}(1, (-1), 1, \dots, (-1)) \in \mathbb{R}^{2k \times 2k}$ . The functions  $f_1, \dots, f_{j-1}, f_{j+1}, \dots, f_{2k}$  (for any  $j = 1, \dots, 2k$ ) generate a Chebyshev system on the interval  $I$  and consequently the quantities  $(-1)^i e_i^T F^{-1} e_j$  have the same sign, which implies that the weights  $w_{i,j}$  are all nonnegative. It now follows from Elfving's theorem (see Elfving (1952)) that the design  $\xi_j^*$  is  $e_j$ -optimal and, from the results of Studden (1968), that  $h_j = c_j^*$ . Finally, the statement (b) is a consequence of recent results of Imhof and Studden (2001) (see their Theorem 2.1(a) and the proof of Theorem 2.1(b)) and its proof is therefore omitted.

Note that Lemma 2.2 yields for all  $b$  that  $\max_\eta \lambda_{\min}(C(\eta, b)) = \lambda_{\min}(C(\xi_E^*, b)) = 1/(2k)$ , and the standardized maximin optimality criterion in (2.8) reduces to the maximization of the function

$$\min_{b \in B} \lambda_{\min}(C(\xi, b)). \tag{2.12}$$

The remaining part of this section is devoted to an equivalence theorem for the optimality criterion (2.12). To this end let  $\Pi$  denote the set of all probability measures defined on a  $\sigma$ -field on  $B$ , which contains all one-point sets. For a pair  $(\xi, \pi)$  (where  $\xi$  is a design on  $I$  and  $\pi \in \Pi$  is a probability measure on  $B$ ), for which the minimum eigenvalue of the matrix  $C(\xi, b)$  has multiplicity one, we define the vector  $p_b = p_b(\xi)$  by the relation

$$p_b^T C(\xi, b) p_b = \lambda_{\min}(C(\xi, b)) \tag{2.13}$$

and introduce the function

$$\Psi(t, \pi) = \int_B |p_b^T f(t, b)|^2 \pi(db). \tag{2.14}$$

**Theorem 2.3.** *Assume that  $B \subset \mathbb{R}^k$  is a compact set and that the assumptions of Lemma 2.2 are satisfied for all  $b \in B$ . If for any design  $\xi$  with at least  $2k$  support points and all  $b \in B$  the minimum eigenvalue of the matrix*

$$C(\xi, b) = K_{1,b}^{-1}M(\xi, 1, b)K_{1,b}^{-1} \quad (2.15)$$

*is simple and positive, then a design  $\xi^*$  is standardized maximin  $E$ -optimal in the model (2.1) if and only if there exists a probability measure  $\pi^* \in \Pi$  such that*

$$\max_{t \in I} \Psi(t, \pi^*) = \min_{b \in B} \lambda_{\min}(C(\xi^*, b)), \quad (2.16)$$

where the function  $\Psi$  is defined by (2.14).

Moreover, if  $\xi^*$  and  $\pi^*$  satisfy the relation (2.16), then the maximum on the left hand side is attained for any  $t \in \text{supp}(\xi^*)$  and the minimum on the right hand side is attained for any  $b \in \text{supp}(\pi^*)$ .

**Proof.** The proof is based on certain standard arguments of approximate optimal design theory and for the sake of brevity we only indicate one direction. Let  $\xi^*$  denote a standardized maximin  $E$ -optimal design and define for  $\alpha \in (0, 1)$ ,  $\xi_\alpha = (1 - \alpha)\xi^* + \alpha\xi_t$ , where  $\xi_t$  puts all mass at the point  $t \in I$ . Introducing  $\phi(\xi, b) = \lambda_{\min}(C_K(\xi, b))$ , we obtain from the optimality of the design  $\xi^*$

$$\min_{b \in B} \phi(\xi_\alpha, b) - \min_{b \in B} \phi(\xi^*, b) \leq 0. \quad (2.17)$$

Next define

$$B^* = \left\{ b \in B \mid \min_{\beta \in B} \phi(\xi^*, \beta) = \phi(\xi^*, b) \right\} \quad (2.18)$$

as the set of points where the minimum of the function  $\phi(\xi^*, \cdot)$  is attained (note that  $B^*$  depends on the design  $\xi^*$ , which is not reflected by our notation) and introduce the function  $Q(\alpha) = \min_{\pi \in \Pi} \int_B \phi(\xi_\alpha, b)\pi(db)$  (again the dependence on  $\pi$  is not reflected by our notation). Defining  $\lambda^* = Q(0) = \min_{b \in B} \phi(\xi^*, b)$  we obtain from (2.17),  $(1/\alpha)\{Q(\alpha) - Q(0)\} = (1/\alpha)\{Q(\alpha) - \lambda^*\} \leq 0$ , which gives in the limit

$$\left. \frac{\partial}{\partial \alpha} Q(\alpha) \right|_{\alpha=0+} = \min_{\pi \in \tilde{\Pi}} \int_B \left. \frac{\partial}{\partial \alpha} \phi(\xi_\alpha, b) \right|_{\alpha=0+} \pi(db) \leq 0. \quad (2.19)$$

Here  $\tilde{\Pi} = \left\{ \pi \in \Pi \mid \int_B \phi(\xi^*, b)\pi(db) = \lambda^* \right\}$ . Now  $\phi(\xi, b) = p_b^T C(\xi, b)p_b$ , where  $p_b$  is the eigenvector of the matrix  $C_K(\xi, b)$  corresponding to the minimum eigenvalue (which has multiplicity 1, by assumption), and therefore we obtain from (2.19) that

$$\min_{\pi \in \tilde{\Pi}} \int_B (p_b^T f(t, b))^2 \pi(db) \leq \lambda^* \quad (2.20)$$

for any  $t$ . On the other hand we have

$$\int_B \int_I (p_b^T f(t, b))^2 \xi^*(dt) \pi(db) = \int_B \phi(\xi^*, b) \pi(db) = \lambda^* \quad (2.21)$$

for any  $\pi \in \tilde{\Pi}$ , which implies  $\max_{t \in I} \int_B (p_b^T f(t, b))^2 \pi(db) \geq \lambda^*$  for any  $\pi \in \tilde{\Pi}$ . Comparing this inequality with (2.20) and observing (2.21) shows the existence of a probability measure  $\pi^*$  such that (2.16) holds. The remaining assertions of the theorem are shown similarly and the proofs are left to the reader.

**Remark 2.4.** The theory developed so far is applicable for a broad class of models including the cases, where the function  $\varphi(t, b)$  in (2.1) is given by  $1/(t + b)$ ,  $e^{-tb}$ ,  $\log(t + b)$ . However, for the explicit determination of the standardized maximin  $E$ -optimal designs, several steps have to be performed which differ for the different models. As a consequence each model has to be investigated separately. We illustrate this procedure for the Michaelis-Menten model in the next section.

### 3. Standardized Maximin $E$ -optimal Designs for the Michaelis-Menten Model

Note that (1.1) is a special case of (2.1) [ $k = 1, \varphi(t) = t/(t + b)$ ]. It is easy to see from (2.9) that the functions

$$f_1(t, b) = \frac{t}{t + b}, \quad f_2(t, b) = \frac{-t}{(t + b)^2} \quad (3.1)$$

generate a Chebyshev system on the interval  $(0, t_0]$  and any single function has the same property on the interval  $(0, t_0]$ . Note that the point  $t = 0$  is obviously not a support of an optimal design for the Michaelis-Menten model (independent of the optimality criterion). Therefore it is sufficient to consider this model only on the interval  $(0, t_0]$  and all assumptions of Lemma 2.2 and Theorem 2.3 are satisfied. A straightforward calculation shows that the Chebyshev polynomial is given by

$$c_1^* f_1(t, b) + c_2^* f_2(t, b), \quad (3.2)$$

where the functions  $f_1$  and  $f_2$  are defined in (3.1), the coefficients and Chebyshev points are given by

$$c_1^* = c_1^*(b) = \frac{t_1^{*2} - b^2}{(t_1^*)^2}, \quad c_2^* = c_2^*(b) = -\frac{c_1^* b (t_1^* + b)}{t_1^* - b}, \quad (3.3)$$

$$t_1^* = t_1^*(b) = \frac{\sqrt{2} t_0 b}{2t_0 + 2b + \sqrt{2}b}; \quad t_2^* = t_0. \quad (3.4)$$



Moreover, from the Cauchy-Binet formula we obtain that, for any design  $\xi$  with at least  $n \geq 2$  support points, the information matrix  $C(\xi, b)$  defined in (2.15) is positive definite. Because it is a  $2 \times 2$  matrix and the element in the position (1, 2) does not vanish it must have a minimum eigenvalue of multiplicity one. The following result is now an immediate consequence of Lemma 2.2.

**Theorem 3.1.**

- (a) For  $j = 1, 2$  the locally  $e_j$ -optimal design for the Michaelis-Menten model is given by

$$\xi_j^* = \begin{pmatrix} t_1^* & t_0 \\ w_j^* & 1 - w_j^* \end{pmatrix}, \quad j = 1, 2, \quad (3.5)$$

where the point  $t_1^*$  is defined in (3.4) and the weight at this point is  $\omega_1 = [(2\sqrt{2} + 3)b] / [(3\sqrt{2} + 4)b + \sqrt{2}t_0]$  or  $\omega_2 = 2^{-1/2}$ .

- (b) A standardized locally  $E$ -optimal design for the Michaelis-Menten model is given by

$$\xi_E^* = \begin{pmatrix} t_1^* & t_0 \\ w^* & 1 - w^* \end{pmatrix}, \quad (3.6)$$

where the point  $t_1^*$  is defined in (3.4) and the weight at this point is  $w^* = [2(3 + 2\sqrt{2})b + t_0] / [2\sqrt{2}((3 + 2\sqrt{2})b + t_0)]$ . Moreover,  $\lambda_{\min}(C(M(\xi_E^*), b)) = 1/2$ .

We now concentrate on the standardized maximin  $E$ -optimality criterion, where the parameter space  $B$  is a “small” interval. In this case it can be proved that the standardized maximin  $E$ -optimal design  $\xi^*$  is always supported at two points. Note that this fact is intuitively clear because in this case the standardized maximin  $E$ -optimal design  $\xi^*$  should be close to a locally standardized  $E$ -optimal design. We mention that this fact has also been observed numerically for Bayesian  $D$ -optimal designs (see Chaloner and Larntz (1989) or Haines (1995)), but to our knowledge a rigorous proof of this property in a non-trivial context is not known.

**Lemma 3.2.** Consider the standardized maximin  $E$ -optimality criterion defined by (2.8) with  $B = [b_0 - \Delta, b_0 + \Delta] \subset \mathbb{R}^+$ ,  $\Delta > 0$  in the Michaelis-Menten model (1.1). If  $\Delta$  is sufficiently small,

- (a) any standardized maximin  $E$ -optimal design for the Michaelis-Menten model on the interval  $[0, t_0]$  is supported at two points including the point  $t_0$ ;  
 (b) any measure  $\pi^*$  defined by the identity (2.16) satisfies  $\text{supp}(\pi^*) = \partial B = \{b_0 - \Delta, b_0 + \Delta\}$ .

**Proof.** For a proof of (a) we assume the contrary. This means that there exists a sequence  $(\Delta_n)_{n \in \mathbb{N}}$  of positive constants converging to zero such that for, any  $n \in \mathbb{N}$ , there exists a standardized maximin  $E$ -optimal design  $\xi_n^*$  for the

Michaelis-Menten model (with  $B_n = [b_0 - \Delta_n, b_0 + \Delta_n]$ ) which has either at least three support points or two support points in the interval  $[0, t_0]$ . Because 0 cannot be a support point,  $\xi_n^*$  has at least two support points, say  $t_{1,n}^*$  and  $t_{2,n}^*$ , in the interval  $(0, t_0)$ . Recalling the definition of the function  $\Psi$  in (2.14) and Theorem 2.3, we obtain for each  $n \in \mathbb{N}$  a probability measure  $\pi_n^*$  such that  $\text{supp}(\pi_n^*) \subset B_n = [b_0 - \Delta_n, b_0 + \Delta_n]$ ,

$$\Psi(t_{i,n}, \pi_n^*) = \lambda_n^* \quad i = 1, 2, \quad \Psi'(t_{i,n}, \pi_n^*) = 0; \quad i = 1, 2, \tag{3.7}$$

where the derivative of  $\Psi(\cdot, \pi_n^*)$  is taken with respect to the first argument and  $\lambda_n^* = \min_{b \in B_n} \lambda_{\min}(C(\xi_n^*, b))$ . A standard argument shows that there exists a subsequence (also denoted by  $\Delta_n$ ) such that  $\lim_{n \rightarrow \infty} t_{i,n} = \bar{t}_i \quad i = 1, 2; \quad \lim_{n \rightarrow \infty} \lambda_n^* = \bar{\lambda}$ . From (3.7) and (2.14) we obtain (note that  $\pi_n^*$  converges weakly to the Dirac measure  $\delta_{b_0}$ )

$$\begin{aligned} \Psi(\bar{t}_i, \delta_{b_0}) &= (p_{b_0}^T f(\bar{t}_i, b_0))^2 = \bar{\lambda}; \quad i = 1, 2 \\ \Psi'(\bar{t}_i, \delta_{b_0}) &= \frac{\partial}{\partial t} (p_{b_0}^T f(t, b_0))^2 \Big|_{t=\bar{t}_i} = 0; \quad i = 1, 2. \end{aligned} \tag{3.8}$$

Now the identity  $f(0, b_0) = 0$  shows that  $\bar{t}_i \neq 0, \quad i = 1, 2$ . Moreover, if  $\bar{t}_1 = \bar{t}_2$ , we would obtain the relations  $\Psi'(\bar{t}_1, \delta_{b_0}) = \Psi''(\bar{t}_1, \delta_{b_0}) = 0, \quad \Psi(\bar{t}_1, \delta_{b_0}) = \bar{\lambda}, \quad \Psi(t, \delta_{b_0}) \leq \bar{\lambda} \quad \forall t \in I$ . This is impossible because  $p_{b_0}^T f(t, b_0)$  is the Chebyshev polynomial. A similar argument shows that  $\bar{t}_2 < t_0$ . Consequently, we obtain  $0 < \bar{t}_1 < \bar{t}_2 < t_0$  and (3.8) yields a contradiction to the Chebyshev property of the system  $\{f_1(t, b), f_2(t, b)\}$  on the interval  $(0, t_0)$ . The conclusion follows.

For a proof of (b) we use Proposition 5.1 in the Appendix. To be precise, let  $s = 2, \quad x = (x_1, x_2)^T = (t, w)^T, \quad y = b$  and define for a design  $\xi_{t,w} = \begin{pmatrix} t & t_0 \\ w & 1-w \end{pmatrix}$ , the function  $G(t, w, b) = \lambda_{\min}(C(\xi, b))$ . Then it is easy to see that  $G$  is twice continuously differentiable and assumption (a) of Proposition 5.1 is obviously satisfied. For a proof of assumption (b) we note that

$$\begin{aligned} G(t, w, b) &= \lambda_{\min}(C(\xi_{t,w}, b)) = \lambda_{\min}(K_b^{-1}M(\xi_{t,w}, 1, b)K_b^{-1}) \\ &= w(\bar{p}_b f_1(t, b))^2 + (1-w)(\bar{p}_b f_2(t_0, b))^2, \end{aligned}$$

where  $\bar{p}_b = K_b^{-1}p_b, \quad p_b$  is an eigenvector of the matrix  $C(\xi_{t,w}, b) = K_b^{-1}M(\xi_{t,w}, 1, b)K_b^{-1}$  corresponding to its minimum eigenvalue, the matrix  $M(\xi_{t,w}, 1, b)$  is defined in (2.2), and the matrix  $K_b = K_{1,b}$  is given by

$$K_b^{-1} = \begin{pmatrix} c_1^*(b) & 0 \\ 0 & c_2^*(b) \end{pmatrix} = \begin{pmatrix} c_1^* & 0 \\ 0 & c_2^* \end{pmatrix} \tag{3.9}$$

with  $c_1^* = c_1^*(b)$  and  $c_2^* = c_2^*(b)$  defined by (3.3) (see Lemma 2.2a). Now the equations

$$\frac{\partial}{\partial t}G(t, w, b) = \frac{\partial}{\partial w}G(t, w, b) = 0 \tag{3.10}$$

yield the system

$$\begin{aligned} w((\bar{p}_b^T f(t, b))^2)' &= 0 \\ (\bar{p}_b^T f(t, b))^2 &= (\bar{p}_b^T f(t_0, b))^2. \end{aligned} \tag{3.11}$$

But this means that  $\bar{p}_b f(t, b)$  must be equal (up to a sign) to the Chebyshev polynomial  $c^{*T} f(t, b) = c_1^* f_1(t, b) + c_2^* f_2(t, b)$  defined by (3.3). Therefore we obtain  $\bar{p}_b = c^*$  and the solution of the first equation in (3.10) with respect to  $t$  is uniquely determined by the interior Chebyshev point  $t = t_1^*$  defined in (3.4). On the other hand, we have  $K_b^{-1}M(\xi_{t,w}, 1, b)\bar{p}_b = \lambda_{\min}(C(\xi_{t,w}, b))K_b\bar{p}_b$  and, inserting  $\bar{p}_b = c^*$ , this also determines the weight  $w$  uniquely. This proves (b) in Proposition 5.1. In fact it follows by these arguments that the unique solution  $t^* = t^*(b)$ ,  $w^* = w^*(b)$  of the system (3.10) is precisely the interior support point and its corresponding weight of the locally standardized  $E$ -optimal design given in part (b) of Theorem 3.1.

Finally, for a proof of (c), at Proposition 5.1, introduce  $x^*(b) = (t^*(b), w^*(b))^T$  and calculate in a straightforward manner

$$\begin{aligned} V &= (x^*(b))^T J(b)x^*(b) \\ &= 2w^*(b) \left( \frac{\partial}{\partial b} t^*(b) \right)^2 \left[ \bar{p}_b^T f(t, b) \frac{\partial^2}{\partial^2 t} \bar{p}_b^T f(t, b) \right] \Big|_{t=t^*(b)}. \end{aligned}$$

Observing the Chebyshev property of the functions  $f_1, f_2$ , and that the Chebyshev polynomial  $\bar{p}_b^T f(t, b) = c^{*T} f(t, b)$  is maximal at  $t = t^*(b)$ , we obtain  $V < 0$ , and the third assumption of Proposition 5.1. Now this proposition shows that for sufficiently small  $\Delta$  and any two point design  $\xi_{t,w}$  the function

$$Q(\xi_{t,w}, b) = \frac{\lambda_{\min}(C(\xi_{t,w}, b))}{\max_{\eta} \lambda_{\min}(C(\eta, b))} = 2\lambda_{\min}(C(\xi_{t,w}, b))$$

is concave as a function of  $b \in B_n = [b_0 - \Delta, b_0 + \Delta]$  (here the last identity follows from Lemma 2.2). Consequently, observing part (a) we obtain for sufficiently small  $\Delta > 0$  that  $\text{supp}(\pi^*) = \{b_0 - \Delta, b_0 + \Delta\}$ , which proves the second part of the assertion.

We conclude this section with a more explicit characterization of the standardized maximin  $E$ -optimal designs for the Michaelis-Menten model in the situation of the previous lemma.

**Theorem 3.3.** *Consider the Michaelis-Menten model (1.1) and the standardized maximin  $E$ -optimality criterion (2.8) with  $B = [b_1, b_2]$  where  $0 < b_1 < b_2$ .*

- (a) For sufficiently small  $b_2 - b_1$  a standardized maximin  $E$ -optimal design is of the form  $\xi^* = \begin{pmatrix} t_1 & t_0 \\ \bar{w} & 1 - \bar{w} \end{pmatrix}$  and the corresponding probability measure  $\pi^*$  in Theorem 2.3 is of the form  $\pi^* = \begin{pmatrix} b_1 & b_2 \\ \bar{\alpha} & 1 - \bar{\alpha} \end{pmatrix}$ . Here  $(t_1, \bar{\alpha}, \bar{w})$  is a solution of the optimization problem  $\max_{t \in T} \max_{t, \alpha \in [0,1]} \min_{\alpha \in [0,1]} g(t, w, \alpha)$ , where the function  $g$  is defined by

$$g(t, w, \alpha) = \alpha \left( u_{b_1} - \sqrt{u_{b_1}^2 - v_{b_1}} \right) + (1 - \alpha) \left( u_{b_2} - \sqrt{u_{b_2}^2 - v_{b_2}} \right),$$

with  $u_b = (1/2) \operatorname{tr}(K_b^{-1} M(\xi_{t,w}, 1, b) K_b^{-1})$  and  $v_b = (\det K_b)^{-2} |M(\xi_{t,w}, 1, b)|$ , and the matrices  $K_b^{-1}$  and  $M(\xi, 1, b)$  are defined in (3.9) and (1.2), respectively.

- (b) The design  $\xi^*$  defined in part (a) is standardized maximin  $E$ -optimal if and only if

$$\max_{t \in [0, t_0]} \bar{\alpha} (p_{b_1}^T f(t, b_1))^2 + (1 - \bar{\alpha}) (p_{b_2}^T f(t, b_2))^2 = \min_{b \in [b_1, b_2]} (u_b - \sqrt{u_b^2 - v_b}).$$

**Proof.** Observing the notation  $C(\xi^*, b_i) = K_{b_i}^{-1} M(\xi^*, b_i) K_{b_i}^{-1}$  ( $i = 1, 2$ ) it is easy to see that  $\lambda_{\min}(C(\xi^*, b_i)) = u_{b_i} - \sqrt{u_{b_i}^2 - v_{b_i}}$ . The proof now follows by a direct application of Lemma 3.2 and Theorem 2.3.

#### 4. A Numerical Example

In this section we take  $[0, t_0] = [0, 10]$  and calculate standardized maximin  $E$ -optimal designs for various sets of the form  $B = [1, b_2]$ . From Theorem 3.3, the optimal designs are supported at two points if  $b_2$  is close to  $b_1 = 1$ . We calculated the optimal two point designs with the aid of the first part of Theorem 3.3 and checked its optimality in the class of all designs by an application of part (b) of that theorem. If  $b_2 = 1, 2, 3, \dots, 7$  the standardized maximin  $E$ -optimal design is in fact supported at only two points and the corresponding designs are depicted in Table 4.1. The table also contains the standardized maximin  $E$ -optimal designs in the class of all standardized locally optimal designs, that is,

$$\xi_{\text{loc}}^* = \operatorname{argmax} \left\{ \min_{b \in B} \frac{\lambda_{\min}(C(\xi, b))}{\max_{\eta} \lambda_{\min}(C(\eta, b))} \mid \xi \in \Xi \right\}, \quad (4.1)$$

where  $\Xi$  denotes the class of all designs defined in part (b) of Theorem 3.1 by (3.6). Note that the determination of these designs is substantially simpler compared to the calculation of the standardized maximin  $E$ -optimal design within the class

of all designs. It is of interest to investigate the corresponding efficiencies of these designs:

$$\text{eff}(\xi) = \min_{b \in B} \frac{\lambda_{\min}(C(\xi, b))}{\max_{\eta} \lambda_{\min}(C(\eta, b))}. \quad (4.2)$$

Table 4.1. The standardized maximin  $E$ -optimal designs for the Michaelis-Menten model on the interval  $[0, 10]$  with  $B = [1, b_2]$ . The table contains the support points  $x_1, x_2$  and weights  $w_1, w_2$  of the design  $\xi^*$  and  $\xi_{\text{loc}}^*$  defined by (2.8) and (4.1), while the minimum efficiency is defined by (4.2). In all cases the standardized maximin  $E$ -optimal design is supported at two points.

	$b_2$	1	2	3	4	5	6	7
$\xi_{\text{loc}}^*$	$x_1$	10	10	10	10	10	10	10
	$x_2$	0.6040	0.8134	0.9602	1.0708	1.1579	1.2286	1.2874
	$w_1$	0.5163	0.4856	0.4670	0.4543	0.4450	0.4378	0.4321
	$w_2$	0.4837	0.5144	0.5330	0.5457	0.5550	0.5622	0.5679
$\xi^*$	$x_1$	10	10	10	10	10	10	10
	$x_2$	0.6040	0.8169	0.9693	1.0847	1.1757	1.2498	1.3111
	$w_1$	0.5163	0.4880	0.4727	0.4625	0.4550	0.4494	0.4449
	$w_2$	0.4837	0.5120	0.5273	0.5375	0.5450	0.5506	0.5551
$\xi_{\text{loc}}^*$	eff	1	0.9544	0.8946	0.8448	0.8050	0.7728	0.7465
$\xi^*$	eff	1	0.9544	0.8947	0.8451	0.8053	0.7733	0.7471

Obviously this quantity is decreasing with increasing values of  $b_2$ , but even when  $b_2 = 7$  the standardized maximin  $E$ -optimal design has an efficiency of 75 %. Moreover, the standardized maximin  $E$ -optimal design  $\xi^*$  and the design  $\xi_{\text{loc}}^*$  obtained by maximizing (2.8) in the subclass  $\Xi$  of all designs defined in Theorem 3.1(b) have nearly the same performance from a practical point of view.

If  $b_2 \geq 8$  it follows from Theorem 3.3 that the best two point design is not optimal within the class of all designs and the standardized maximin  $E$ -optimal design has at least three support points. Some representative results are depicted in Table 4.2, which also contains the two point designs obtained from the first part of Theorem 3.3 and the designs  $\xi_{\text{loc}}^*$  defined by (4.1). Our numerical results show that for  $b_2 \geq 8$  the standardized maximin  $E$ -optimal design is always supported at three points. We observe that the two point designs are quite efficient compared to standardized maximin  $E$ -optimal designs supported at three points. For example in the case  $b_2 = 20$ , the two point designs yield approximately 60% at (4.2), while the standardized maximin  $E$ -optimal design  $\xi^*$  gives a minimal efficiency of approximately 67 %. Only for very large values is the difference

between the two and three point designs notable (see the columns with  $b_2 = 50$  and  $b_2 = 100$  in Table 4.2).

Table 4.2. The standardized maximin  $E$ -optimal designs for the Michaelis-Menten model on the interval  $[0, 10]$  with  $B = [1, b_2]$ . The table contains the support points  $x_i$  and weights  $w_i$  of the design  $\xi^*$  and  $\xi_{\text{loc}}^*$  defined by (2.8) and (4.1) and the best two-point design  $\xi_{\text{two}}^*$  defined in the first part of Theorem 3.3, while the minimum efficiency is defined by (4.2). In all cases the standardized maximin  $E$ -optimal design is supported at three points.

	$z_2$	8	10	12	14	16	18	20	50	100
$\xi_{\text{loc}}^*$	$x_1$	10	10	10	10	10	10	10	10	10
	$x_2$	1.3371	1.4166	1.4777	1.5262	1.5657	1.5984	1.6261	1.8030	1.8753
	$w_1$	0.4275	0.4203	0.4151	0.4111	0.4079	0.4053	0.4032	0.3902	0.3853
	$w_2$	0.5725	0.5797	0.5849	0.5889	0.5921	0.5947	0.5968	0.6098	0.6147
$\xi_{\text{two}}^*$	$x_1$	10	10	10	10	10	10	10	10	10
	$x_2$	1.3630	1.4464	1.5103	1.5610	1.6023	1.6367	1.6660	1.8508	1.9266
	$w_1$	0.4413	0.4358	0.4317	0.4286	0.4262	0.4243	0.4228	0.4130	0.4094
	$w_2$	0.5587	0.5642	0.5683	0.5714	0.5738	0.5757	0.5772	0.5870	0.5906
$\xi^*$	$x_1$	10	10	10	10	10	10	10	10	10
	$x_2$	1.0985	0.9278	0.8757	0.8396	0.8105	0.7965	0.7974	0.8647	0.9119
	$x_3$	2.3340	2.8343	3.1096	3.3276	3.5114	3.6534	3.7205	4.0054	4.1907
	$w_1$	0.4262	0.4002	0.3835	0.3711	0.3603	0.3520	0.3487	0.3362	0.3320
	$w_2$	0.4060	0.3549	0.3456	0.3398	0.3363	0.3350	0.3341	0.3353	0.3377
	$w_3$	0.1678	0.2449	0.2709	0.2890	0.3034	0.3130	0.3172	0.3285	0.3303
$\xi_{\text{loc}}^*$	eff	0.7246	0.6904	0.6649	0.6452	0.6295	0.6167	0.6060	0.5417	0.5172
$\xi_{\text{two}}^*$	eff	0.7253	0.6911	0.6657	0.6461	0.6304	0.6176	0.6070	0.5429	0.5185
$\xi^*$	eff	0.7270	0.7034	0.6906	0.6829	0.6779	0.6745	0.6720	0.6562	0.6499

From these results (and similar results not given) we draw the following conclusions. Only in cases with nearly no prior information about the unknown parameter can the effort of calculating the standardized maximin  $E$ -optimal design within the class of all designs be justified. In all other cases the two point designs obtained in Theorem 3.3 and the two point designs defined in (4.1) have a very similar performance as the standardized maximin  $E$ -optimal designs. In many cases the designs from Theorem 3.3 are already standardized maximin  $E$ -optimal as can be checked by the second part of Theorem 3.3. On the other hand the designs defined by (4.1) are practically indistinguishable from the designs in Theorem 3.3, and substantially simpler to calculate. Therefore, if it can be assumed that the parameter  $b$  varies in an interval  $[b_1, b_2]$  which is not too large,

these designs provide a reasonable compromise between efficiently designing an experiment for the Michaelis-Menten model and dealing with the complexity of a non-differentiable optimization problem.

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**Appendix**

**Proposition A.1.** *Let  $G : \Omega \times I \rightarrow R$ , where  $\Omega \subset \mathbb{R}^s$  is a compact set and  $I \subset \mathbb{R}$  an arbitrary interval. Assume that the following conditions are satisfied.*

- (a) *The function  $G$  is positive and twice continuously differentiable.*
- (b) *For any  $y \in I$ ,  $\frac{\partial}{\partial x}G(x, y) = \left(\frac{\partial}{\partial x_1}G(x, y), \dots, \frac{\partial}{\partial x_s}G(x, y)\right)^T = 0$  has a unique solution  $x^* = x^*(y)$  in  $\Omega$ .*
- (c) *For all  $y \in I$  we have  $(x^*(y))^T J(y)x^*(y) < 0$ , where for fixed  $y \in I$   $J(y) = \left(\frac{\partial^2}{\partial x_i \partial x_j}G(x, y)\right)_{x=x^*(y)}^s_{i,j=1}$  is the Jacobian of  $G$  evaluated at the point  $(x^*(y), y)$ .*

*For any fixed  $x \in \Omega$  the function  $Q(y) = Q(x, y) = G(x, y)/(\max_{\bar{x} \in \Omega} G(\bar{x}, y))$  is twice continuously differentiable with respect to  $y$  and, if  $x$  is sufficiently close to  $x^*(y)$ , we have  $Q''(y) < 0$ .*

**Proof.** A straightforward calculation shows

$$\frac{\partial}{\partial y}G(x^*(y), y) = \frac{\partial}{\partial y}G(x, y)\Big|_{x=x^*(y)} + \sum_{i=1}^s \frac{\partial}{\partial x_i}G(x, y)\Big|_{x=x^*(y)} \cdot \frac{\partial}{\partial y}(x_i^*(y)). \quad (A.1)$$

Observing condition (b) we obtain

$$\begin{aligned} \frac{\partial^2}{\partial^2 y}G(x^*(y), y) &= \frac{\partial^2}{\partial^2 y}G(x, y)\Big|_{x=x^*(y)} \\ &\quad - \sum_{i,j=1}^s \frac{\partial^2}{\partial x_i \partial x_j}G(x, y)\Big|_{x=x^*(y)} \frac{\partial}{\partial y}x_i^*(y) \frac{\partial}{\partial y}x_j^*(y). \end{aligned} \quad (A.2)$$

The second derivative of the function  $Q$  (with respect to  $y$ ) is  $\frac{\partial^2}{\partial^2 y}Q(y) = \frac{\partial^2}{\partial^2 y}Q(x, y) = Q_1(x, y) + Q_2(x, y)$ , where the functions  $Q_1, Q_2$  are defined by

$$Q_1(x, y) = \frac{\frac{\partial^2}{\partial^2 y}G(x, y)H(y) - G(x, y)H''(y)}{H^2(y)},$$

$$Q_2(x, y) = -\frac{2H'(y)\{\frac{\partial}{\partial y}G(x, y)H(y) - G(x, y)H'(y)\}}{H^3(y)},$$

and  $H(y) = \max_{\bar{x} \in \Omega} G(\bar{x}, y) = G(x^*(y), y)$ . From (A.1) and condition (b) we have  $H'(y) = \frac{\partial}{\partial y}G(x, y)\Big|_{x=x^*(y)}$ , which implies  $Q_2(x^*(y), y) = 0$ . Similarly, using (A.2), it follows that  $Q_1(x^*(y), y) = [(x^*(y))^T J(y)x^*(y)]/H^2(y) < 0$  by assumption (c). Consequently for any  $x \in \Omega$  the function  $Q$  is twice continuously differentiable and, if  $\bar{x}$  is sufficiently close to  $x^*(y)$ ,  $Q''(y) = Q''(\bar{x}, y) < 0$ .

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Ruhr-Universität Bochum, Fakultät für Mathematik, 44780 Bochum, Germany.

E-mail: holger.dette@ruhr-uni-bochum.de

St. Petersburg State University, Department of Mathematics, St. Petersburg, Russia.

E-mail: v.melas@pobox.spbu.ru

St. Petersburg State University, Department of Mathematics, St. Petersburg, Russia.

E-mail: andrey@ap7236.spb.edu

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