Supplementary Material to ‘Optimal designs for active controlled dose finding trials with efficacy-toxicity outcomes’

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A. APPENDIX 1: PROOFS

A.1. Characterization of admissible designs

A set of $k+1$ real-valued continuous functions $u_0, \ldots, u_k$ defined on $[L, R]$ is called a Tchebycheff system on the interval $[L, R]$ if the inequality $\det(u_i(d_j))_{i,j=0}^k > 0$ holds for all $L \leq d_0 < d_1 < \ldots < d_k \leq R$. Note that we can rewrite the information matrix $M_1(\xi, \theta_1)$ in the form

$$M_1(\xi, \theta_1) = \begin{pmatrix} \int_L^R \psi_{11}(d) d\xi(d) & \ldots & \int_L^R \psi_{1s_1}(d) d\xi(d) \\ \vdots & \ddots & \vdots \\ \int_L^R \psi_{s_11}(d) d\xi(d) & \ldots & \int_L^R \psi_{s_1s_1}(d) d\xi(d) \end{pmatrix},$$

(A1)

where we ignore the dependence of the functions $\psi_{ij}$ on the parameter $\theta_1$. We now define $\psi_0(d) \equiv 1$ and choose a basis, say $\{\psi_0, \ldots, \psi_k\}$, for the space $\text{span}\{\psi_{ij} : 1 \leq i, j \leq s_1\} \cup \{1\}$. We further assume that $\psi_k$ is one of the diagonal elements of $M_1(\xi, \theta_1)$, does not coincide with any of the other elements $\psi_{ij}$ and that $\{\psi_0, \ldots, \psi_{k-1}\}$ is a basis of the space $\text{span}\{\psi_{ij} : i, j \in \{1, \ldots, s_1\}; \psi_{ij} \neq \psi_k\} \cup \{1\}$.

Our next result, Theorem A1, is a more general version of Theorem 3.1 in Dette & Melas (2011) that is specific to our problem here. The proof is quite similar to the one given in this reference and is omitted for the sake of brevity. Theorem A1 yields better bounds on the number of support points of optimal designs obtained from the current literature. Such examples are given in Theorem 3 and we refer to its proof at the end of Section A.2, where we explain the differences between Theorem A1 and Theorem 3.1 in Dette & Melas (2011).

THEOREM A1.

(a) If $\{\psi_0, \psi_1, \ldots, \psi_{k-1}\}$ and $\{\psi_0, \psi_1, \ldots, \psi_k\}$ are Tchebycheff systems on the interval $D$, then for any design $\xi$ there exists a design $\xi^+$ with at most $(k+2)/2$ support points, such that $M_1(\xi^+, \theta_1) \geq L M_1(\xi, \theta_1)$. If $I(\xi) < k/2$, then the design $\xi^+$ is uniquely determined in the class of...
all designs \( \nu \) satisfying

\[
\int_{L}^{R} \psi_i(d) d\nu(d) = \int_{L}^{R} \psi_i(d) d\xi(d), \quad i = 0, \ldots, k - 1
\]

and coincides with the design \( \xi \). Otherwise, the following two assertions hold.

(i) If \( k \) is odd, then \( \xi^+ \) has at most \((k + 1)/2\) support points and \( \xi^+ \) can be chosen such that its support contains the point \( R \).

(ii) If \( k \) is even, then \( \xi^+ \) has at most \( k/2 + 1 \) support points and \( \xi^+ \) can be chosen such that its support contains the points \( L \) and \( R \).

(b) If \( \{\psi_0, \psi_1, \ldots, \psi_{k-1}\} \) and \( \{\psi_0, \psi_1, \ldots, -\psi_k\} \) are Tchebycheff systems, then for any design \( \xi \) there exists a design \( \xi^- \) with at most \((k + 2)/2\) support points, such that \( M_1(\xi^-, \theta_1) \geq_{L} M_1(\xi, \theta_1) \). If \( I(\xi) < k/2 \), then the design \( \xi^- \) is uniquely determined in the class of all designs \( \eta \) satisfying (A2) and coincides with the design \( \xi \). Otherwise, the following assertions hold.

(i) If \( k \) is odd, then \( \xi^- \) has at most \((k + 1)/2\) support points and \( \xi^- \) can be chosen such that its support contains the point \( L \).

(ii) If \( k \) is even, then \( \xi^- \) has at most \( k/2 + 1 \) support points.

Theorem A1 provides information about the admissible designs. For example, consider the case \((a)(ii)\) with \( k = 2m \) for some \( m \in \mathbb{N} \). Any design \( \xi \) with index \( I(\xi) \geq m \) can be improved with respect to the Loewner ordering by a design with at most \( m + 1 \) support points that includes the boundary points \( L \) and \( R \). It follows that admissible designs are designs with index \( < m \) and designs with \( m + 1 \) support points that include the boundary points \( L \) and \( R \) of the design space.

A.2. Proofs of Theorems 2 and 3

We present the proof of Theorem 3 only for the case, where the effect of the drug on efficacy and toxicity is modeled by an Emax model. In this case the gradient of the outcome with respect to the parameter is given by

\[
\frac{\partial}{\partial \theta_1} \eta_1(d, \theta_1) = \begin{pmatrix}
\frac{d}{\theta_2 + d} - \frac{\theta_1^2 d}{(\theta_2 + d)^2} & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & \frac{d}{\theta_2 + d} - \frac{\theta_1^2 d}{(\theta_2 + d)^2}
\end{pmatrix}.
\]

It is easy to see that there exists a full column rank matrix \( L \in \mathbb{R}^{6 \times 10} \) which does not depend on the variable \( d \) such that

\[
\frac{\partial}{\partial \theta_1} \eta_1(d, \theta_1) = \begin{pmatrix}
\nu^T(d) & 0 \\
0 & \nu^T(d)
\end{pmatrix} L^T,
\]

where the vector \( \nu(d) \) is defined by the linearly independent functions in the gradient, i.e.

\[
\nu(d) = (1, \frac{1}{\theta_2 + d}, \frac{1}{(\theta_2 + d)^2}, \frac{1}{\theta_2 + d}, \frac{1}{(\theta_2 + d)^2})^T \in \mathbb{R}^5.
\]

Consequently, we obtain for the information matrix in (3) the representation

\[
M_1(\xi, \theta_1) = L \int_{\mathcal{D}} \begin{pmatrix}
\nu(d) \nu^T(d) & 0 \\
0 & \nu(d) \nu^T(d)
\end{pmatrix} d\xi(d)L^T,
\]

where the matrix 0 is the \( 5 \times 5 \) matrix with all entries 0 and

\[
\nu(d) \nu^T(d) = \begin{pmatrix}
1 & \frac{1}{\theta_2 + d} & \frac{1}{(\theta_2 + d)^2} & \frac{1}{\theta_2 + d} & \frac{1}{(\theta_2 + d)^2} \\
\frac{1}{\theta_2 + d} & \frac{1}{\theta_2 + d} & \frac{1}{\theta_2 + d} & \frac{1}{(\theta_2 + d)^2} & \frac{1}{(\theta_2 + d)^2} \\
\frac{1}{(\theta_2 + d)^2} & \frac{1}{(\theta_2 + d)^2} & \frac{1}{(\theta_2 + d)^2} & \frac{1}{(\theta_2 + d)^2} & \frac{1}{(\theta_2 + d)^2} \\
\frac{1}{\theta_2 + d} & \frac{1}{(\theta_2 + d)^2} & \frac{1}{(\theta_2 + d)^2} & \frac{1}{(\theta_2 + d)^2} & \frac{1}{(\theta_2 + d)^2} \\
\frac{1}{\theta_2 + d} & \frac{1}{(\theta_2 + d)^2} & \frac{1}{(\theta_2 + d)^2} & \frac{1}{(\theta_2 + d)^2} & \frac{1}{(\theta_2 + d)^2}
\end{pmatrix}.
\]
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Now Theorem 14.2.9 in Harville (1997) shows that an improvement with respect to the Loewner ordering can be obtained by improving the common block
\[
\int_D \nu(d)\nu^T(d)d\xi(d)
\]
in the matrix (A3). For this purpose we now use Theorem A1. The functions \(\psi_0(d) = 1\) and
\[
\psi_1(d) = \frac{1}{\sigma_1^2 + d}, \quad \psi_2(d) = \frac{1}{\sigma_2^2 + d}, \quad \psi_3(d) = \frac{1}{\sigma_3^2 + d}, \quad \psi_4(d) = \frac{1}{\sigma_4^2 + d},
\]
fulfill the conditions specified in the paragraph before Theorem A1. It follows by an application of Theorem 1.1 in Chapter IX of Karlin & Studden (1966) that the sets \(\{\psi_0, \ldots, \psi_7\}\) and \(\{\psi_0, \ldots, \psi_8\}\) are Tchebycheff systems and Theorem A1 is applicable with \(k = 8\). Part (a)(ii) of this result yields that there exists a design \(\xi^*\) with at most five support points including \(L\) and \(R\) such that
\[
\int_D \nu(d)\nu^T(d)d\xi^*(d),
\]
and the assertion follows. We note that an application of Theorem 3.1 in Dette & Melas (2011) is not possible because the different functions from matrix (A4) do not form a Tchebycheff system.

A.3. Proof of Theorem 4

Let \(\xi\) be a minimally supported design of the form (8). As \(s^*_1 = s^*_1\) we have \(k = s^*_1 + 1\). Considering the Cholesky decomposition \(\Sigma_1^{-1} = \tilde{\Sigma}\tilde{\Sigma}^T\) of the inverse of the covariance matrix \(\Sigma_1\) we obtain for the information matrix \(M_1(\xi, \theta_1)\) the representation
\[
M_1(\xi, \theta_1) = \sum_{i=1}^{k} \omega_i \left( \frac{\partial}{\partial \theta_i} \eta_1(d_i, \theta_1) \right)^T \tilde{\Sigma} \tilde{\Sigma}^T \left( \frac{\partial}{\partial \theta_1} \eta_1(d_i, \theta_1) \right)
= G^T\text{Diag}(\omega_1, \omega_2, \ldots, \omega_k)G,
\]
where the matrix \(G\) is defined by
\[
G = \begin{pmatrix}
\tilde{\Sigma}^T \left( \frac{\partial}{\partial \theta_1} \eta_1(d_1, \theta_1) \right) \\
\vdots \\
\tilde{\Sigma}^T \left( \frac{\partial}{\partial \theta_1} \eta_1(d_k, \theta_1) \right)
\end{pmatrix} = \begin{pmatrix}
I_k \otimes \tilde{\Sigma}^T \\
\vdots \\
I_k \otimes \tilde{\Sigma}^T
\end{pmatrix} \left( \frac{\partial}{\partial \theta_1} \eta_1(d_1, \theta_1) \right),
\]
and \(A \otimes B\) denotes the Kronecker product of the matrices \(A\) and \(B\). Now
\[
\det \{M_1(\xi, \theta_1)\} = (\det G)^2 \prod_{j=1}^{k} \omega_j^2
\]
and consequently, the minimally supported \(D\)-optimal design must have equal weights. Moreover, the representation
\[
\det(G) = \det(\tilde{\Sigma})^k \det \left[ \left( \frac{\partial}{\partial \theta_1} \eta_1(d_j, \theta_1) \right)_{j=1, \ldots, k} \right]
\]
shows that the support points of the minimally supported \(D\)-optimal design do not depend on the elements of the matrix \(\Sigma_1\). This completes the proof of Theorem 4.

A.4. Proof of Theorem 5

We show only the proof of part 1(a) as the proofs for other cases are similar. If two Michaelis-Menten models are used to describe the effect of the drug on efficacy and toxicity, at least two support points, say \(d_1, d_2\), are necessary to guarantee invertibility of the information matrix. From Theorem 4, it follows that
Assume that the model for efficacy is given by

$$\omega^*_1 = \omega^*_2 = 1/2$$

and a direct calculation yields for the determinant of the information matrix of an equally weighted design $\xi$

$$\det\{M_1(\xi, \theta_1)\} = \frac{(\vartheta_1^1 \vartheta_1^1)^2}{4 \det(\Sigma)} \frac{d_1^2 d_2^2 (d_2 - d_1)^4}{(\vartheta_2^1 + d_1)^2 (\vartheta_2^1 + d_2)^2 (\vartheta_2^2 + d_2)^2 (\vartheta_2^2 + d_2)^2}.$$  \hspace{1cm} (A5)

Without loss of generality, we assume $d_1 < d_2$, whereupon the right hand side of (A5) becomes a monotone function of $d_2$. Consequently, the right boundary point $R$ is one of the optimal support points, that is $d_2 = R$. Maximizing the remaining expression with respect to the point $d_1$ in the interval $[L, R]$ gives

$$d_1 = \max \left\{L, \frac{R \vartheta_2^2 (R + \vartheta_2^1 + \vartheta_2^2) + (\vartheta_2^2 \vartheta_2^2)^2} {R + \vartheta_2^2 + \vartheta_2^2} \right\}$$

which proves the result. \hfill \Box

\textbf{A.5. Proof of Theorem 6}

Assume that $\tilde{\xi}$ is not admissible, that is there exists a design

$$\tilde{\eta} = \left( (\tilde{d}_1, 0) \ldots (\tilde{d}_l, 0) \ (C, 1) \right)$$

such that $M(\tilde{\eta}, \theta_1) \neq M(\tilde{\xi}, \theta_1)$ and $M(\tilde{\eta}, \theta_1) \geq L M(\tilde{\xi}, \theta_1)$. This yields immediately $\bar{\omega}_{l+1} \geq \tilde{\omega}_{k+1}$ and

$$(1 - \bar{\omega}_{l+1}) M_1(\eta, \theta_1) \geq (1 - \tilde{\omega}_{k+1}) M_1(\xi, \theta_1),$$

where $\eta$ denotes the design with masses $\omega_1/(1 - \bar{\omega}_{l+1}), \ldots, \omega_l/(1 - \bar{\omega}_{l+1})$ at the points $\tilde{d}_1, \ldots, \tilde{d}_l$, respectively. Therefore we obtain

$$(1 - \bar{\omega}_{l+1}) M_1(\eta, \theta_1) \geq L (1 - \tilde{\omega}_{k+1}) M_1(\tilde{\xi}, \theta_1) \geq L (1 - \bar{\omega}_{l+1}) M_1(\xi, \theta_1).$$

Because the design $\xi$ is admissible we have $M_1(\eta, \theta_1) = M_1(\xi, \theta_1)$. Using the block structure of the information matrix and the assumption that the design $\tilde{\xi}$ is not admissible it follows that

$$(\bar{\omega}_{l+1} - \tilde{\omega}_{k+1}) M_1(\xi, \theta_1) \leq 0 \text{ and } (\tilde{\omega}_{k+1} - \bar{\omega}_{l+1}) \mathcal{I}(\theta_2) \leq 0.$$  \hspace{1cm} (A5)

This yields $\bar{\omega}_{l+1} = \tilde{\omega}_{k+1}$ and $M(\tilde{\eta}, \theta_1) = M(\tilde{\xi}, \theta_1)$, which is a contradiction to the assumption that the design $\tilde{\xi}$ is not admissible. The desired result follows. \hfill \Box

\textbf{B. Appendix 2: Additional results for the exponential model}

In this section we provide additional results for exponential models. The first result provides upper bounds on the number of support points of optimal designs for models for efficacy and toxicity outcomes without an active control, while the minimally supported optimal designs are presented in Theorem B2. The proofs are similar to those presented in Section A and therefore omitted.

\textbf{Theorem B1.} Assume that the model for efficacy is given by $\eta_1^c(d, \theta_1^c) = \vartheta_0^c + \vartheta_1^c \{ \exp(d/\vartheta_2^c) - 1 \}$ and let $\xi$ denote an arbitrary design on the dose interval $D = [L, R]$.

(a) If $\eta_1^c(d, \theta_1^c) = \vartheta_0^c + \vartheta_1^c d + \vartheta_2^c d^2$, there exists a design $\xi^*$ with at most six support points, such that $M_1(\xi^*, \theta_1) \geq L M_1(\xi, \theta_1)$. If $I(\xi) \geq 5$, $\xi^*$ can be chosen such that its support contains $L$ and $R$.

(b) If $\eta_1^c(d, \theta_1^c) = \vartheta_0^c + \vartheta_1^c \{ \exp(d/\vartheta_2^c) - 1 \}$ with $\vartheta_2^c \notin \{ \vartheta_2^c, 2 \vartheta_2^c, 0.5 \vartheta_2^c \}$, there exists a design $\xi^*$ with at most seven support points, such that $M_1(\xi^*, \theta_1) \geq L M_1(\xi, \theta_1)$.

(c) If $\eta_1^c(d, \theta_1^c) = \vartheta_2^c d(\vartheta_2^c + d)^{-1}$ or $\eta_1^c(d, \theta_1^c) = \vartheta_0^c + \vartheta_1^c d(\vartheta_2^c + d)^{-1}$, there exists a design $\xi^*$ with at most nine support points, such that $M_1(\xi^*, \theta_1) \geq L M_1(\xi, \theta_1)$.

\textbf{Theorem B2.} Assume that the model for efficacy is given by $\eta_1^c(d, \theta_1^c) = \vartheta_0^c + \vartheta_1^c \{ \exp(d/\vartheta_2^c) - 1 \}$.
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(a) If \( \eta_1(x, \theta_1^*) = \theta_0^* + \theta_1^* d + \theta_2^* d^2 \), the minimally supported D-optimal design is a three-point design with equal masses at the points \( L, x^* \) and \( R \), where \( x^* \) is the solution of the equation \( g_{\text{quad}}(x, \theta_2^*) = -g_\text{exp}(x, \theta_2^*) \), where \( g_{\text{quad}}(x, \theta) = \frac{R + L - 2x}{(x - L)(R - x)} \) and

\[
g_{\text{exp}}(x, \theta) = \frac{\exp((L+x)/\theta)(x-L)+\exp((R+x)/\theta)(R-x)+\exp((L-x)/\theta)(x-R)}{\exp((L-x)/\theta)(x-L)+\exp((R+x)/\theta)(R-x)+\exp((L-x)/\theta)(x-R)}.
\]

(b) If \( \eta_1(x, \theta_1^*) = (\theta_0^* + \theta_1^* d)(\theta_2^* + d) \), the minimally supported D-optimal design is a three-point design with equal masses at the points \( L, x^* \) and \( R \), where \( x^* \) is the solution of the equation \( g_{\text{max}}(x, \theta_2^*) = -g_{\text{exp}}(x, \theta_2^*) \), where \( g_{\text{max}}(x, \theta) = \{R(\theta - x) + L(2R + \theta - x) - 2\theta x\} \{\{x - L\}(R - x)(\theta + x)\}^{-1} \) and \( g_{\text{exp}}(x, \theta) \) is defined by (B1).

(c) If \( \eta_1(x, \theta_1^*) = \theta_0^* + \{\exp(d/\theta_2^*) - 1\} + \theta_2^* \neq \theta_2^* \), the minimally supported D-optimal design is a three-point design with equal masses at the points \( L, x^* \) and \( R \), where \( x^* \) is the solution of the equation \( g_{\text{exp}}(x, \theta) = -g_{\text{exp}}(x, \theta_2^*) \), where \( g_{\text{exp}}(x, \theta) \) is defined by (B1). If \( \eta_1(x, \theta_1^*) = \theta_0^* + \{\exp(d/\theta_2^*) - 1\} + \theta_2^* = \theta_2^* \), the minimally supported D-optimal design is a three-point design with equal masses at the points \( L, \{R - \theta_2^* \exp(R/\theta_2^*) - L \exp(L/\theta_2^*)\} \{\exp(R/\theta_2^*) - \exp(L/\theta_2^*)\}^{-1} \) and \( R \).

C. Appendix 3: Additional Examples

In this section we provide several additional examples illustrating our approach. In particular we analyse designs for a clinical trial investigating Angiotensin-converting enzyme (ACE) inhibitors to treat hypertension and congestive heart failure.

Example C1. Suppose that the mean outcome for toxicity is given by an Emax model. We consider two situations, where the efficacy outcome is first modeled by an Emax model and in the second case, is modeled by the Michaelis-Menten model. For the first case, it follows from Theorem 3 that admissible designs in active controlled trials are of the form (7) with at most six support points and the minimally supported designs in trials without an active control have at most five support points. By Theorem 6, we conclude that there exists an admissible design for the corresponding active controlled trial with at most six support points with a positive weight \( \omega_6 \in (0, 1) \) for the active control. Similarly, for the second case, it also follows from Theorem 3 that there exists an admissible design for the corresponding active controlled trial with at most six support points with a positive weight \( \omega_6 \in (0, 1) \) for the active control. Moreover, the dose levels for the new drug include the boundary points \( L \) and \( R \) of the dose interval.

Example C2. Assume that the effect of the drug on efficacy and toxicity are both studied using Emax models. The minimally supported D-optimal design for model (9) with an active control (10) can be obtained from Theorem 3 and Theorem 7. We set \( s_1 = 6 \) and Theorem 5 provides the support points of the minimally supported D-optimal design for the dose response model (9). Theorem 7 yields \( \omega_6 = 1/4 \) for the proportion of patients treated with the active control. Additionally, the minimally supported D-optimal design for model (9) with an active control (10) allocates the rest of the patients equally to the new drug at 3 dose levels given by

\[
L, \quad \frac{((L + \theta_2^*)(R + \theta_2^*)(L + \theta_2^*)(R + \theta_2^*))^{1/2} + LR - \theta_2^* \theta_2^*}{L + R + \theta_2^* + \theta_2^*} \quad \text{and} \quad R.
\]

Example C3. Tao et al. (2015) analysed data from a clinical trial to treat hypertension and congestive heart failure. They used an Emax-model with parameters \( \theta_1^* = (2.5, 14.5, 0.2)^T \) for the mean efficacy outcome and an exponential model with parameters \( \theta_1^* = [0.2, 0.037, 1/\{3.3 \log(6)\}] \) to model the toxicity effects [see Table 1 in this reference]. As described in Section 3.3.1 of Tao et al. (2015), they used a uniform design to allocate patients to the dose levels 0, 0.05, 0.2, 0.4, 0.6, 0.8, and 1, respectively. For the error distribution in model (1) they assumed a two dimensional centered normal distribution with parameters \( \rho = 0.4, \sigma_x = 7 \) and \( \sigma_y = 8 \). We use this information to determine a locally D-optimal design for the active controlled trial. Note that we do not require information from the model for the active
Table 1. Locally $D$-optimal design and minimally supported $D$-optimal design for a case study in Tao et al. (2015).

<table>
<thead>
<tr>
<th>$D$-optimal design</th>
<th>minimally supported $D$-optimal design</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0-00, 0)</td>
<td>(0, 0)</td>
</tr>
<tr>
<td>(0-16, 0)</td>
<td>(0-63, 0)</td>
</tr>
<tr>
<td>(0-84, 0)</td>
<td>(0, 0)</td>
</tr>
<tr>
<td>(1-00, 0)</td>
<td>(1, 0)</td>
</tr>
<tr>
<td>(C, 1)</td>
<td>(C, 1)</td>
</tr>
</tbody>
</table>

By Theorem B1(c) and Theorem 6, we only need to consider designs with at most ten support points. We first used the particle swarm optimization algorithm to generate the locally $D$-optimal design for model (1) and in the second step, applied Theorem 7 to determine the locally optimal design for the model with an active control. The results are shown in Table 1. The locally $D$-optimal design has five support points and is therefore not minimally supported. The optimality of the design for the new drug was checked by Theorem 1. Figure 1 displays the sensitivity function of the locally $D$-optimal design which confirms its optimality.

The minimally supported $D$-optimal design can be obtained from Theorem B2(b) and is shown in the right part of Table 1. The $D$-efficiency of the minimally supported design is given by 0.7006. The good performance of the minimally supported design is also confirmed by calculating the $D$-efficiency of the uniform design used in Tao et al. (2015) relative to our locally $D$-optimal design and the minimally supported $D$-optimal design. These relative efficiencies are 0.8294 and 1.2031, respectively. Although the minimally supported design has less support points than the design used in Tao et al. (2015) it has almost the same efficiency.
REFERENCES


