Optimal designs for dose response curves with common parameters

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Motivating Example

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- Situation: A new drug is developed.
- Two typical questions might be:
  1. What is the minimally effective dose?
  2. Should the drug be taken daily or weekly?
- We use a dose finding study to answer these questions.

Idea: Describe the dose response curve of the daily dosage for instance by

$$f(d, \theta^{(1)}) = \theta_1^{(1)} + \frac{\theta_2^{(1)} d}{\theta_3^{(1)} + d}$$

Describe the dose response curve of the weekly dosage for instance by

$$f(d, \theta^{(2)}) = \theta_1^{(2)} + \frac{\theta_2^{(2)} d}{\theta_3^{(2)} + d}$$

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Motivating Example

$$f(d,\theta^{(1)}) = \theta_1^{(1)} + \frac{\theta_2^{(1)} d}{\theta_3^{(1)} + d} \quad f(d,\theta^{(2)}) = \theta_1^{(2)} + \frac{\theta_2^{(2)} d}{\theta_3^{(2)} + d}$$

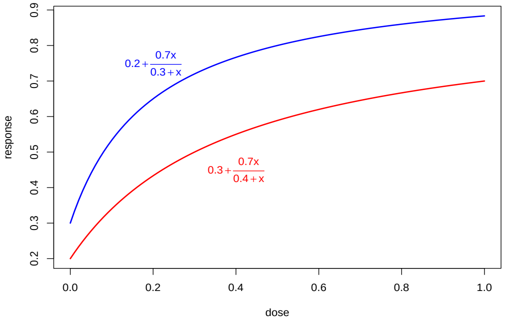

Figure: *Two Emax curves.*

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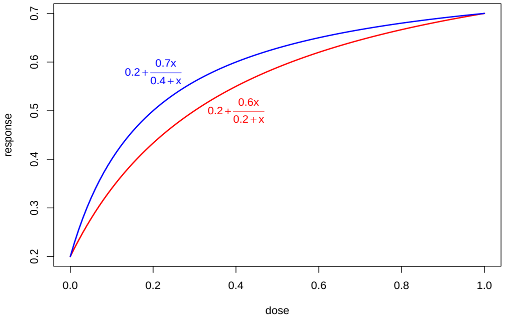

Figure: *Two Emax curves where the placebo effect is the same.*

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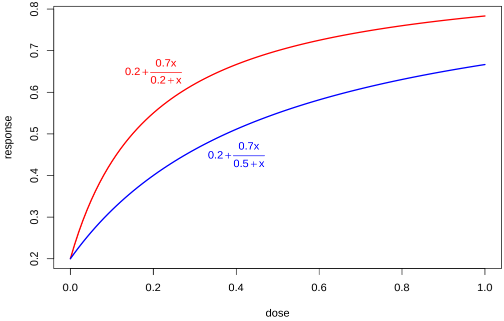

Figure: *Two Emax curves where the placebo effect and the Emax effect is the same.*

Model formulation

- 2 dose response curves (from 2 samples)

$$Y_{ij\ell} = f(d_j^{(i)}, \theta_1, \theta_2^{(i)}) + \varepsilon_{ij\ell} \quad \begin{array}{c} i = 1,2 \\ j = 1,\ldots,k_i \\ \ell = 1,\ldots,n_{ij} \end{array}$$

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- $\theta_1 \in \mathbb{R}^p$ same parameter in each group
- $\theta_2^{(i)} \in \mathbb{R}^q$ different parameter in each group
- $d_j^{(i)} \in \mathcal{X}_i = [0, d_{\max}^{(i)}]$
- $n_i = \sum_{j=1}^{k_i} n_{ij}$ for $i = 1, 2$ and $N = n_1 + n_2$
- $\varepsilon_{ij\ell} \sim \mathcal{N}(0, \sigma_i^2)$ independent

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Complete parameter in the two models

$$\theta = (\theta_1, \theta_2^{(1)}, \theta_2^{(2)}) \in \mathbb{R}^{p+2q}$$

Example: Two Emax models

What does this notation look like for the Emax models?

Example: Two Emax models

$$f(d, \theta_1, \theta_2^{(i)})$$

Common Placebo

$$\theta_1 + \frac{\vartheta_1^{(i)} d}{\vartheta_2^{(i)} + d}$$

$$\theta = (\theta_1, \vartheta_1^{(1)}, \vartheta_2^{(1)}, \vartheta_1^{(2)}, \vartheta_2^{(2)})^T \in \mathbb{R}^5$$

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$$\theta = (\vartheta_1, \vartheta_2, \theta_2^{(1)}, \theta_2^{(2)})^T \in \mathbb{R}^4$$

Task

Find optimal designs for estimating the parameter

$$\theta = (\theta_1, \theta_2^{(1)}, \theta_2^{(2)}) \in \mathbb{R}^{p+2q}$$

most precisely!

Maximum Likelihood Estimator (MLE)

The designs for **two** samples (of sizes n_1 and n_2)

$$\xi_1^N = \begin{pmatrix} d_1^{(1)} & \cdots & d_{k_1}^{(1)} \\ \frac{n_{11}}{n_1} & \cdots & \frac{n_{1k_1}}{n_1} \end{pmatrix}, \xi_2^N = \begin{pmatrix} d_1^{(2)} & \cdots & d_{k_2}^{(2)} \\ \frac{n_{21}}{n_2} & \cdots & \frac{n_{2k_2}}{n_2} \end{pmatrix}, \lambda^N = \begin{pmatrix} 1 & 2 \\ \frac{n_1}{N} & \frac{n_2}{N} \end{pmatrix}$$

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Further assumption:

$$\lim_{N\to\infty} \frac{n_i}{N} = \lambda_i \in (0,1) \qquad \text{and} \qquad \lim_{n_i\to\infty} \frac{n_{ij}}{n_i} = \xi_{ij} \in (0,1)$$

Then the MLE $\hat{\theta} = (\hat{\theta}_1, \hat{\theta}_2^{(1)}, \hat{\theta}_2^{(2)})$ satisfies as $N \to \infty$

$$\sqrt{N}(\hat{\theta} - \theta) \xrightarrow{\mathcal{D}} \mathcal{N}(0, M^{-1}(\xi, \theta)),$$

where $\xi = (\xi_1, \xi_2, \lambda)$.

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The structure of the information matrix

The information matrix of the design $\xi = (\xi_1, \xi_2, \lambda)$

$$M(\xi, \theta) = \lambda_1 M^{(1)}(\xi_1, \theta) + \lambda_2 M^{(2)}(\xi_2, \theta) \in \mathbb{R}^{(p+2q)\times(p+2q)}$$

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where the matrices $M^{(i)}(\xi_i, \theta)$ are defined by

$$M^{(i)}(\xi_i, \theta) = \int_{\mathcal{X}_i} h_i(d) h_i^T(d) d\xi_i(d)$$

and $h_i^T(d)$ is the gradient of $f(d, \theta_1, \theta_2^{(i)})$ w.r.t. θ

$$h_1^T(d) = \frac{1}{\sigma_1}\Big(\tfrac{\partial}{\partial\theta_1} f(d, \theta_1, \theta_2^{(1)}), \tfrac{\partial}{\partial\theta_2^{(1)}} f(d, \theta_1, \theta_2^{(1)}), 0_q^T\Big)$$
$$h_2^T(d) = \frac{1}{\sigma_2}\Big(\tfrac{\partial}{\partial\theta_1} f(d, \theta_1, \theta_2^{(2)}), 0_q^T, \tfrac{\partial}{\partial\theta_2^{(2)}} f(d, \theta_1, \theta_2^{(2)})\Big)$$

The Emax cases

1. The same placebo effect: $\theta = (\theta_1, \vartheta_1^{(1)}, \vartheta_2^{(1)}, \vartheta_1^{(2)}, \vartheta_2^{(2)})^T$

$$h_1^T(d) = \frac{1}{\sigma_1}\left(1, \frac{d}{\vartheta_2^{(1)}+d}, -\frac{\vartheta_1^{(1)}d}{(\vartheta_2^{(1)}+d)^2}, 0, 0\right)$$

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2. The same placebo effect θ_1 and the $E_{\max}$ value: $\theta = (\vartheta_1, \vartheta_2, \theta_2^{(1)}, \theta_2^{(2)})^T$

$$h_1^T(d) = \frac{1}{\sigma_1}\left(1, \frac{d}{\theta_2^{(1)}+d}, -\frac{\vartheta_2 d}{(\theta_2^{(1)}+d)^2}, 0\right)$$

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Remark:
We will restrict ourselves to the two Emax models. The results are also available for a wider class of models.

Once again: the Emax cases

$$f(d, \theta_1, \theta_2^{(i)})$$

Common Placebo

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$$\vartheta_1 + \frac{\vartheta_2 d}{\theta_2^{(i)} + d}$$

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Upper bound for the Emax model

Theorem

Let (w.l.o.g.) $r = \frac{\sigma_1^2}{\sigma_2^2} \leq 1$. *If the regression model is given by one of the cases of the Emax model, then there exists a design* $\xi^+ = (\xi_1^+, \xi_2^+, \lambda^+)$ *with at most* $2 \times 2 + 1 = 5$ *support points such that for all designs* $\xi = (\xi_1, \xi_2, \lambda)$ *(with more than* 5 *support points) it holds*

$$M(\xi^+, \theta) \geq_L M(\xi, \theta).$$

ξ^+ *can be chosen such that*

$$\begin{array}{rcl} |supp(\xi_1^+)| & = & 3 \quad with \quad 0,\ d_{\max}^{(1)} \in supp(\xi_1^+) \\ |supp(\xi_2^+)| & = & 2 \quad with \quad d_{\max}^{(2)} \in supp(\xi_2^+). \end{array}$$

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The Emax cases: The same placebo effect

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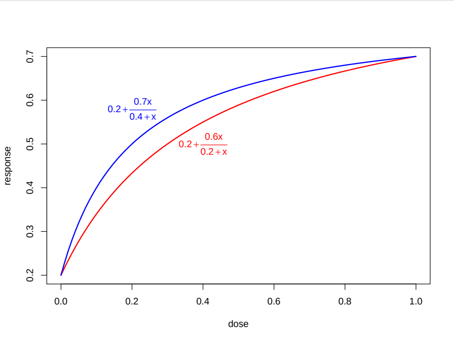

D-optimal design for models with the same placebo

Theorem

Let (w.l.o.g.) $r = \frac{\sigma_1^2}{\sigma_2^2} \leq 1$. *The locally D-optimal design for the Emax model with common placebo effect is of the form* $\xi^* = (\xi_1^*, \xi_2^*, \lambda^*)$, *where*

$$\xi_1^* = \begin{pmatrix} 0 & x^{*,(1)} & d_{\max}^{(1)} \\ \frac{1}{3} & \frac{1}{3} & \frac{1}{3} \end{pmatrix}, \quad \xi_2^* = \begin{pmatrix} x^{*,(2)} & d_{\max}^{(2)} \\ \frac{1}{2} & \frac{1}{2} \end{pmatrix}, \quad \lambda^* = \begin{pmatrix} 1 & 2 \\ \frac{3}{5} & \frac{2}{5} \end{pmatrix}$$

and the point $x^{*,(i)}$ *is given by*

$$x^{*,(i)} = \frac{\vartheta_2^{(i)} d_{\max}^{(i)}}{d_{\max}^{(i)} + 2\vartheta_2^{(i)}} \quad (i = 1, 2).$$

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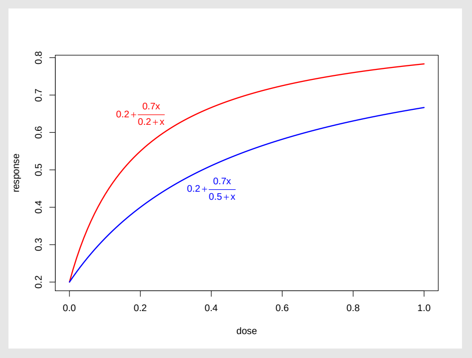
The Emax cases: The same placebo and Emax

$f(d, \theta_1, \theta_2^{(i)})$



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Locally D-optimal design for models with the same placebo and the same $E_{\max}$

- For that case the calculation is more difficult.
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  2. we calculate the saturated D-optimal design under that constraint

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Locally D-optimal design for models with the same placebo and the same E_{max}

- For that case the calculation is more difficult.
- We first calculate the saturated D-optimal design, i.e.
  1. we fix the number of support points of the design ξ to 4
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  3. we check under which circumstances the saturated D-optimal design is also the D-optimal design

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Locally D-optimal design for models with the same placebo and the same $E_{\max}$

Theorem

Let $r = \frac{\sigma_1^2}{\sigma_2^2} \leq 1$, $\bar{\theta}_2^{(i)} = \frac{\theta_2^{(i)}}{d_{\max}^{(i)}}$, $i = 1, 2$ *and* $0 < \bar{\theta}_2^{(1)} < \bar{\theta}_2^{(2)} < 1$. *The locally D-optimal design* $\xi^* = (\xi_1^*, \xi_2^*, \lambda^*)$ *for the Emax model with the same placebo and* $E_{\max}$ *parameter in the class of all saturated designs is given by*

$$\xi_1^* = \begin{pmatrix} 0 & x^{*,(1)} & d_{\max}^{(1)} \\ \frac{1}{3} & \frac{1}{3} & \frac{1}{3} \end{pmatrix}, \quad \xi_2^* = \begin{pmatrix} \theta_2^{(2)} \\ 1 \end{pmatrix}, \quad \lambda^* = \begin{pmatrix} 1 & 2 \\ \frac{3}{4} & \frac{1}{4} \end{pmatrix}. \tag{1}$$

Moreover, $x^{*,(1)}$ *is defined by* $x^{*,(1)} = \frac{\theta_2^{(1)} d_{\max}^{(1)}}{d_{\max}^{(1)} + 2\theta_2^{(1)}}$.

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Locally D-optimal design for models with the same placebo and the same $E_{\max}$

Theorem

Let $r = \frac{\sigma_1^2}{\sigma_2^2} \leq 1$. *Let* $\bar{\theta}_2^{(i)} = \frac{\theta_2^{(i)}}{d_{\max}^{(i)}}$, $i = 1, 2$ *and assume* $0 < \bar{\theta}_2^{(1)} < \bar{\theta}_2^{(2)} < 1$. *The design* ξ^* *defined in* (1) *is locally D-optimal if the condition*

$$\bar{\theta}_2^{(2)} \geq \frac{r\left(6\bar{\theta}_2^{(1)}(\bar{\theta}_2^{(1)}+1)(2\bar{\theta}_2^{(1)}+1)^2\right) - (1-r)}{(6 + 2r\bar{\theta}_2^{(1)}(1 + 2\bar{\theta}_2^{(1)}))} \tag{2}$$

is satisfied.

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D-optimal design for models with the same placebo and the same $E_{\max}$

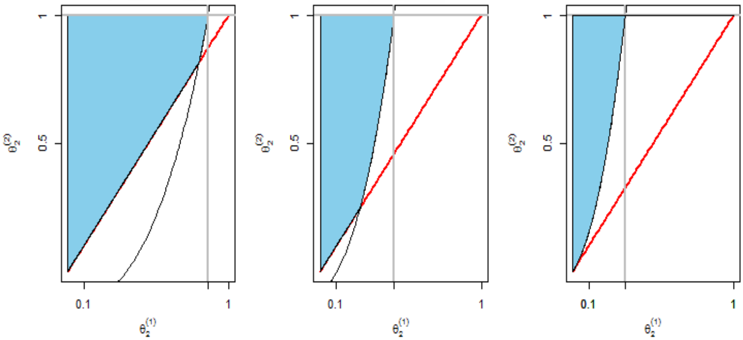

Figure: *The domain where the saturated D-optimal design is also D-optimal for $r = \frac{1}{10}$ (left panel), for $r = \frac{1}{2}$ (middle panel) and $r = 1$ (right panel).*

The Emax case: Explicite parameter values I

We now consider three possible values for the Emax parameter:

$$\theta_A = (0.2, 0.7, 0.2, 0.5)^T,\ \theta_B = (0.2, 0.7, 0.2, 0.3)^T,\ \theta_C = (0.2, 0.7, 0.2, 0.25)^T$$

Moreover, we consider $\mathcal{X}_1 = \mathcal{X}_2 = [0, 1]$ and we set

$$1.\ r = \tfrac{1}{10}, \quad 2.\ r = \tfrac{1}{2}, \quad 3.\ r = 1.$$

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Parameter	Saturated locally D-optimal designs					
	ξ_1^*			ξ_2^*	λ^*	
θ_A	0.00	0.14	1.00	0.50	1	2
	$33.\bar{3}$	$33.\bar{3}$	$33.\bar{3}$	100.0	75.0	25.0
θ_B	0.00	0.14	1.00	0.30	1	2
	$33.\bar{3}$	$33.\bar{3}$	$33.\bar{3}$	100.0	75.0	25.0
θ_C	0.00	0.14	1.00	0.25	1	2
	$33.\bar{3}$	$33.\bar{3}$	$33.\bar{3}$	100.0	75.0	25.0

The Emax case: Explicite parameter values II

$\theta_A = (0.2, 0.7, 0.2, 0.5)^T$, $\theta_B = (0.2, 0.7, 0.2, 0.3)^T$, $\theta_C = (0.2, 0.7, 0.2, 0.25)^T$.

For $r = \frac{1}{10}$ and $r = \frac{1}{2}$ inequality (2) holds:
The saturated D-optimal designs are also D-optimal among all designs.

The Emax case: Explicite parameter values II

$\theta_A = (0.2, 0.7, 0.2, 0.5)^T$, $\theta_B = (0.2, 0.7, 0.2, 0.3)^T$, $\theta_C = (0.2, 0.7, 0.2, 0.25)^T$.

For $r = \frac{1}{10}$ and $r = \frac{1}{2}$ inequality (2) holds:
The saturated D-optimal designs are also D-optimal among all designs.
For the case $r = 1$ we get:

Parameter	Locally D-optimal designs for $r = 1$						
	ξ_1^{*D}			ξ_2^{*D}		λ^{*D}	
θ_A	0.00	0.14	1.00	0.50		1	2
	$33.\bar{3}$	$33.\bar{3}$	$33.\bar{3}$	100.0		75.0	25.0
θ_B	0.00	0.15	1.00	0.26	1.00	1	2
	35.2	33.9	30.9	76.5	23.5	71.0	29.0
θ_C	0.00	0.15	1.00	0.21	1.00	1	2
	36.9	34.7	28.4	68.6	31.4	67.7	32.3

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The efficiencies

The efficiencies for the saturated D-optimal designs are:

Parameter	Efficiency		
	$r = \frac{1}{10}$	$r = \frac{1}{2}$	$r = 1$
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$\theta_B = (0.2, 0.7, 0.2, 0.3)^T$	100 %	100 %	86 %
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Conclusion:

- The saturated D-optimal designs are not always the D-optimal ones, but nevertheless quite efficient.

Further results and outlook

- We also derived results for:
  - $M \geq 2$ groups (i.e. twice daily, daily, weekly, monthly, ...).
  - models of the form

$$f(d, \theta_1, \theta_2^{(i)}) = \theta_1 + \vartheta_{21}^{(i)} f_0(d, \vartheta_{21}^{(i)})$$

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  - the loglinear and the exponential model.
- We applied our results to a dose finding study where we also calculated robust designs.
- We are currently working on the analytical determination of bayesian designs.

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Thank you very much!

References:

Feller, C., Schorning, K., Dette, H., Bermann, G. und Bornkamp, B.(2017+): Optimal designs for dose response curves with common parameters. To appear in: *Annals of Statistics.*

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- For instance the bound for the Emax model (separate) is 3 with the additional information to measure in 0 and $d_{\max}$.
- Prove: All weights for the support point 0 can be put to the design of the group whose variance is smaller.