HELSE BERGEN
Haukeland University Hospital

Dose finding studies: Optimal designs for the Emax model

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Stockholm University

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2. Optimal Designs for the Emax model
3. D-optimal Designs for multi-response Emax models
4. c-optimal Designs for the bivariate Emax model

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↖ Can/Should be addressed with optimal design theory

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We formally define a design ξ, as a set of pairs noted by

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

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and let χ denote the design space, the set of possible doses.

Example

The design $\xi = \left\{ \begin{array}{cc} 0\text{mg} & 100\text{mg} \\ 0.5 & 0.5 \end{array} \right\}$ allocates 50% of the patients to placebo and 50% to 100 mg of the drug?

Optimal Designs for dose response studies

Which designs are optimal?

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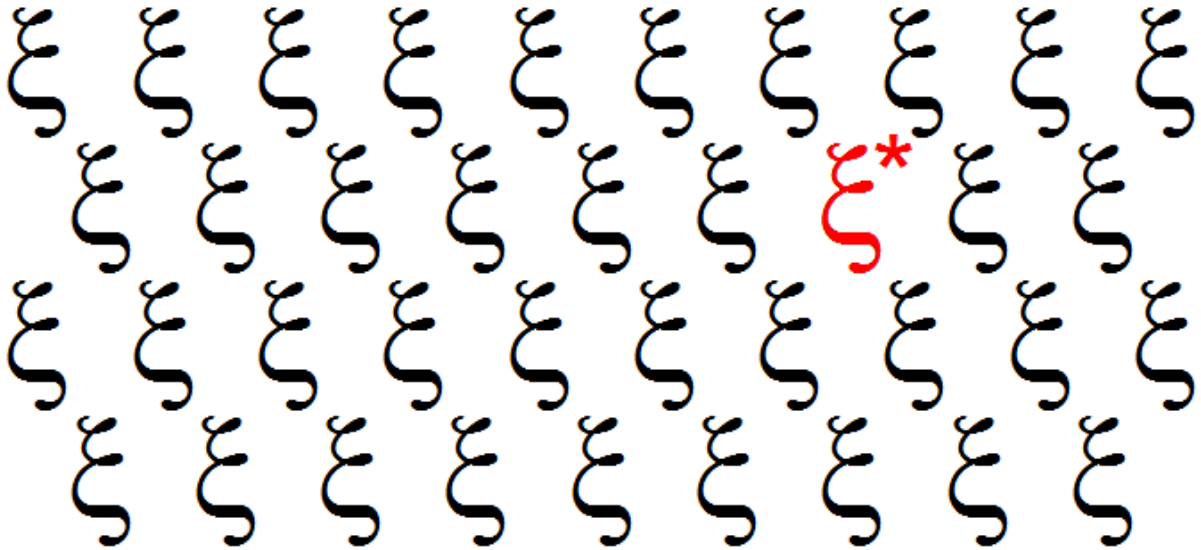
Which designs are optimal?



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Example

If we have a model with only one parameter, θ, and the primary aim of the study is to estimate θ then $\Psi = \text{var}(\hat{\theta})$.

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↖ D-optimality criterion

Optimal Designs for dose response studies

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- $\Psi_D(\xi, \theta) := |M(\xi)^{-1}|$ where $M(\xi)$ is the standardized information matrix, $M(\xi) = N^{-1} I(\xi)$.

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c-optimal designs are appropriate when the objective of the study is to estimate a function, $g(\theta)$, of the model parameters.

- $\Psi_c(\xi, \theta) := \nabla g^T(\theta) M^{-1}(\xi, \theta) \nabla g(\theta)$

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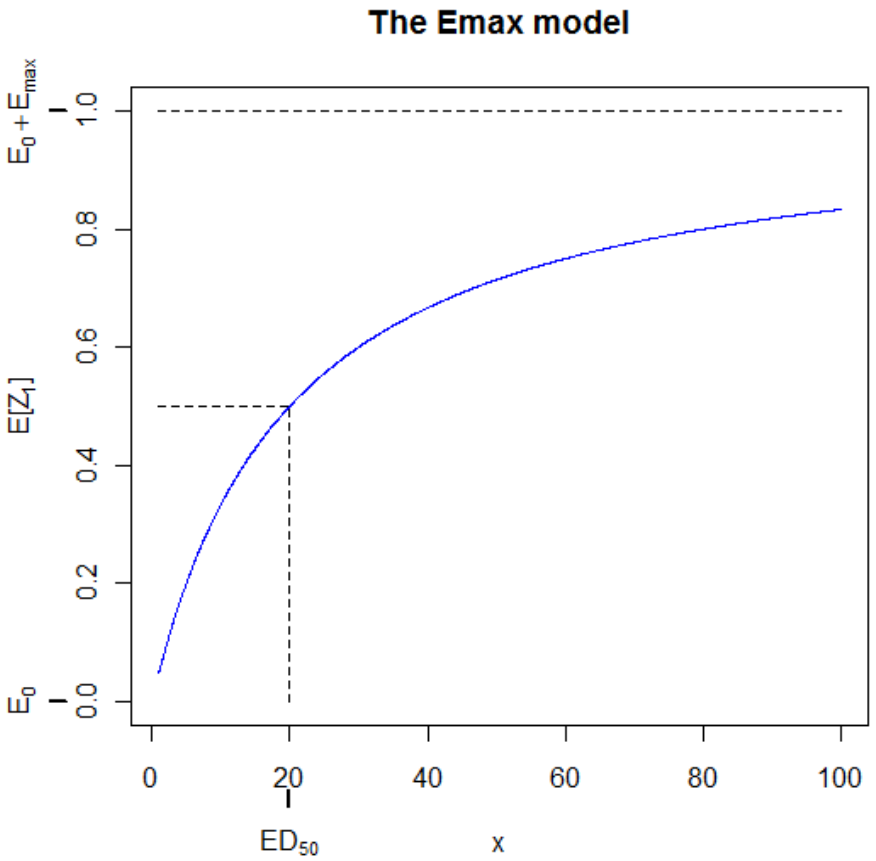
Optimal Designs for the Emax model

Among the most successful dose response models for modeling continuous response is the **Emax model**.



$$\mathrm{E}[Z_1] = E_0 + E_{max}\frac{x}{x + ED_{50}}$$

Figure 1: The Emax model with parameters $E_0 = 0$, $ED_{50} = 20$ and $E_{max} = 1$

Optimal Designs for the Emax model

Example

The design $\xi^* = \left\{ \begin{array}{c} ED_{50} \\ 1 \end{array} \right\}$ is D-optimal (minimizes $\Psi = \text{var}(\hat{ED}_{50})$) for the one parameter Emax model

$$y = \frac{x}{x + ED_{50}} + \epsilon, \qquad x \geq 0, \quad ED_{50} \geq 0, \quad \epsilon \sim N(0, \sigma^2).$$

Optimal Designs for the Emax model

Example

The design $\xi^* = \left\{ \begin{array}{ccc} 0 & ED_{50} & \infty \\ 1/3 & 1/3 & 1/3 \end{array} \right\}$ is D-optimal for the Emax model

$$y = E_0 + E_{max}\frac{x}{x + ED_{50}} + \epsilon, \qquad x \geq 0, \qquad ED_{50} \geq 0, \qquad \epsilon \sim N(0, \sigma^2).$$

Optimal Designs for the Emax model

Example

The design $\xi^* = \left\{ \begin{array}{ccc} 0 & s_b ED_{50} & b \\ 1/3 & 1/3 & 1/3 \end{array} \right\}$ with $s_b := \frac{b/ED_{50}}{2+(b/ED_{50})}$ is D-optimal for the Emax model

$$y = E_0 + E_{max} \frac{x}{x + ED_{50}} + \epsilon, \qquad x \in [0, b], \qquad ED_{50} \geq 0, \qquad \epsilon \sim N(0, \sigma^2).$$

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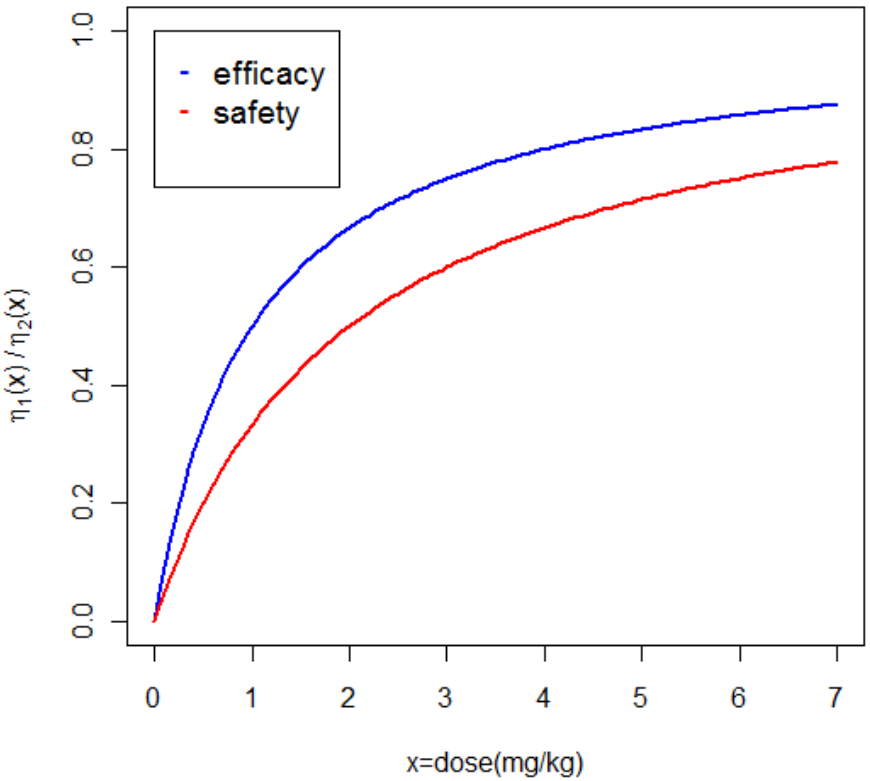
D-optimal Designs for multi-response Emax models

The Emax model can be extended to higher dimension. An example is a bivariate Emax model.



$$\begin{pmatrix} Z_1 \\ Z_2 \end{pmatrix} = \begin{pmatrix} E_{max} \frac{x}{x+ED_{50}} \\ S_{max} \frac{x}{x+SD_{50}} \end{pmatrix} + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix},$$

$$(\epsilon_1, \epsilon_2) \sim \mathcal{N}_2(0, \Sigma),$$

$$\Sigma = \begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}.$$

Σ is assumed to be known.

Figure 2: The Bivariate Emax model with parameters $ED_{50} = 2$ and $E_{max} = SD_{50} = S_{max} = 1$.

D-optimal Designs for multi-response Emax models

Another example is a four dimensional Emax model.

$$\begin{pmatrix} y_{1i} \\ y_{2i} \\ y_{3i} \\ y_{4i} \end{pmatrix} = \begin{pmatrix} E_{max,1} \frac{x_i}{x_i + ED_{50,1}} \\ E_{max,2} \frac{x_i}{x_i + ED_{50,2}} \\ E_{max,3} \frac{x_i}{x_i + ED_{50,3}} \\ E_{max,4} \frac{x_i}{x_i + ED_{50,4}} \end{pmatrix} + \begin{pmatrix} \varepsilon_{1i} \\ \varepsilon_{2i} \\ \varepsilon_{3i} \\ \varepsilon_{4i} \end{pmatrix}, \qquad x \in [0, b], \quad \begin{pmatrix} \varepsilon_{1i} \\ \varepsilon_{2i} \\ \varepsilon_{3i} \\ \varepsilon_{4i} \end{pmatrix} \sim \mathcal{N}_4(0, \Sigma),$$

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- Deriving closed formed optimal designs for this model is very challenging.

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- Deriving closed formed optimal designs for this model is very challenging.
- The designs will depend upon the ED_{50} parameters, the design space χ and on Σ.

D-optimal Designs for multi-response Emax models

A practical example

A phase II clinical study was performed by AstraZeneca to evaluate efficacy, safety and tolerability of the glucokinase activator AZD1656 as add-on treatment to Metformin in type 2 diabetes mellitus (T2DM) patients.

$$x = \text{dose of the glucokinase activator AZD1656}$$

$y_1 =$ change in **HbA1c** from baseline

$y_2 =$ change in **Triglycerides (TG)** from baseline

$y_3 =$ change in **Fasting Plasma Glucose (FPG)** from baseline

$y_4 =$ change in **Total Cholesterol (TC)** from baseline

D-optimal Designs for multi-response Emax models

In the study the allocation of patients to dose groups was

$$\xi = \left\{ \begin{array}{cccccccc} 0 & 10 & 20 & 40 & 50 & 100 & 140 & 200 \\ 82/N & 14/N & 57/N & 49/N & 15/N & 20/N & 59/N & 46/N \end{array} \right\} \quad (1)$$

with $N = 342$.

Table: Emax models are fitted to the complete analysis set.

Variable	Parameter	Estimate	Std. Error
y_1 (HbA1c)	$ED_{50,1}$	83.23	73.21
	$E_{max,1}$	1.16	0.43
y_2 (TG)	$ED_{50,2}$	27.61	32.58
	$E_{max,2}$	0.20	0.07
y_3 (FPG)	$ED_{50,3}$	234.07	512.01
	$E_{max,3}$	0.30	0.40
y_4 (TC)	$ED_{50,4}$	47.30	69.86
	$E_{max,4}$	0.07	0.04

D-optimal Designs for multi-response Emax models

A locally D-optimal design for the study looks as follows:

$$\xi^* = \left\{ \begin{array}{cc} 39.4427 & 200 \\ 1/2 & 1/2 \end{array} \right\} \tag{2}$$

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$$\xi^* = \left\{ \begin{array}{cc} 39.4427 & 200 \\ 1/2 & 1/2 \end{array} \right\} \tag{2}$$

- Is this design sensitive to misspecification of model parameters?

D-optimal Designs for multi-response Emax models

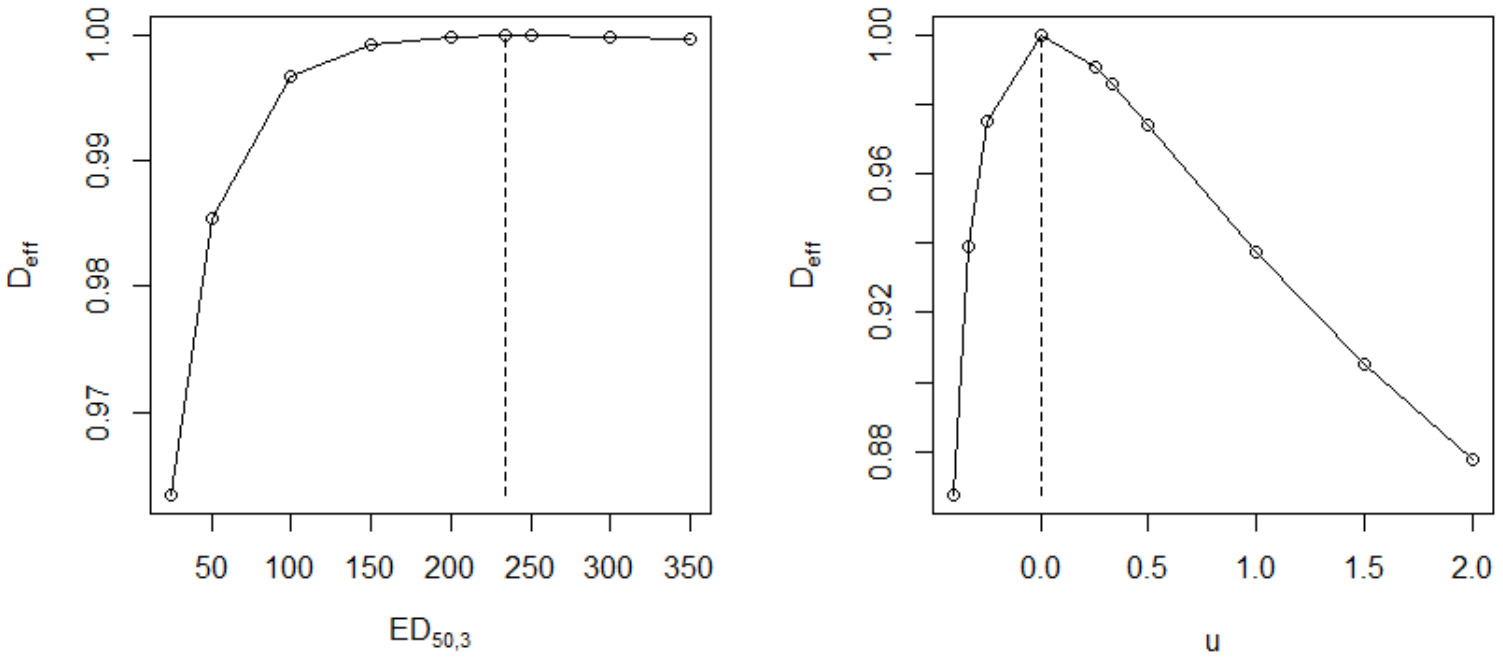

Figure: The efficiency of the design ξ^* in (2). The plot to the left shows the efficiency for different true values of $ED_{50,3}$ when other parameters are assumed to be correctly specified. The plot to the right shows the efficiency as all the ED_{50} parameters are changed by u standard errors.

D-optimal Designs for multi-response Emax models

Definition

The efficiency of a design ξ relative to a D-optimal design ξ_D^* is defined as

$$D_{\text{eff}}(\xi, \theta) = \left(\frac{\Psi_D(\xi_D^*, \theta)}{\Psi_D(\xi, \theta)} \right)^{1/p}.$$

D-optimal Designs for multi-response Emax models

- The design used in the diabetes dose response study is only 61.8% efficient compared to the D-optimal design in (2).

D-optimal Designs for multi-response Emax models

- The design used in the diabetes dose response study is only 61.8% efficient compared to the D-optimal design in (2).
- In order to get the same precision for the parameter estimates in the multi-response Emax model a study allocating patients according to (1) needs $1/0.618 \approx 1.618$ times more patients than a study allocating patients as in (2).

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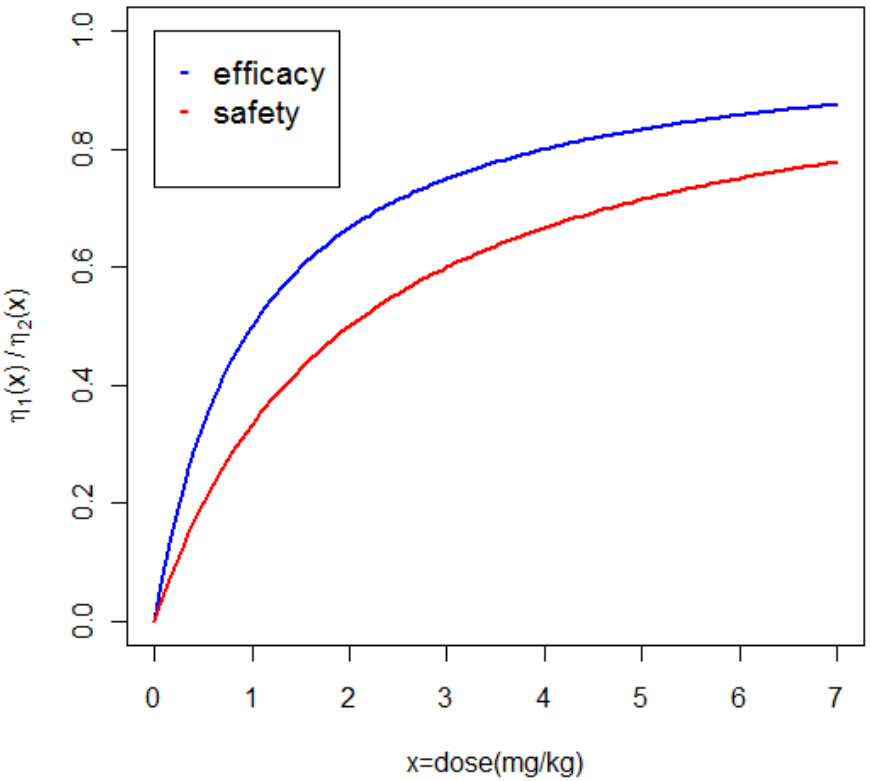
c-optimal Designs for the bivariate Emax model

We extend the Emax model to two dimensions, one for an efficacy variable, Z_1, and one for a safety variable, Z_2.



$$\begin{pmatrix} Z_1 \\ Z_2 \end{pmatrix} = \begin{pmatrix} E_{max} \frac{x}{x+ED_{50}} \\ S_{max} \frac{x}{x+SD_{50}} \end{pmatrix} + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix},$$

$$(\epsilon_1, \epsilon_2) \sim \mathcal{N}_2(0, \Sigma),$$

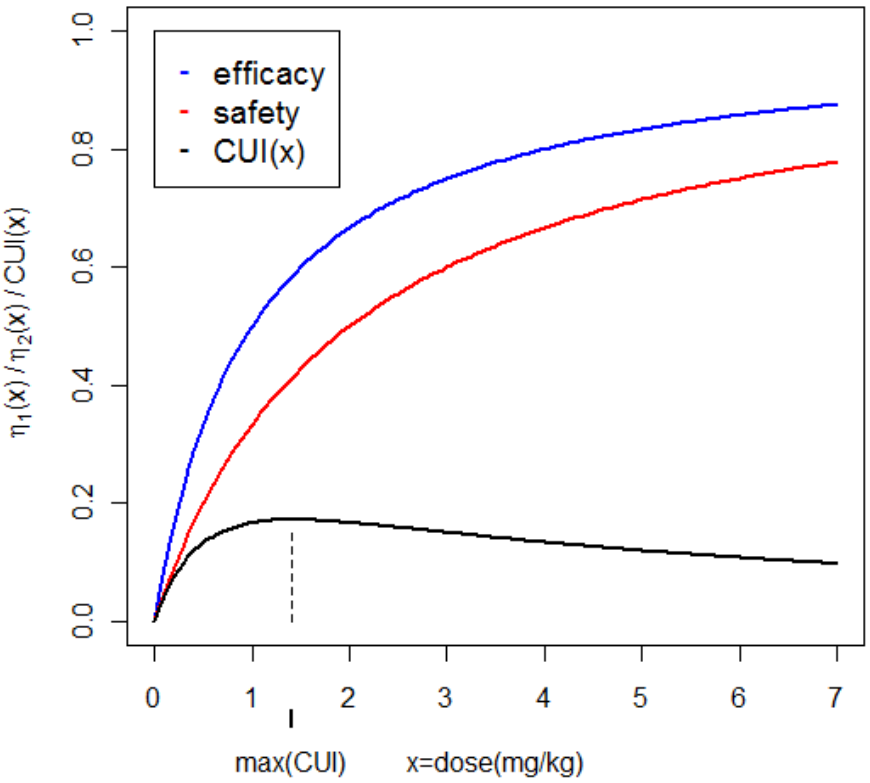
$$\Sigma = \begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}.$$

Σ is assumed to be known.

Figure 2: The Bivariate Emax model with parameters $ED_{50} = 2$ and $E_{max} = SD_{50} = S_{max} = 1$.

c-optimal Designs for the bivariate Emax model

We want to find an optimal design for finding the best dose of the drug i.e. the dose that maximizes the net benefit from taking the drug. The Clinical Utility Index (CUI) is here used to model the net benefit.



$$\text{CUI}(x) = v_1 \text{E}[Z_1] - v_2 \text{E}[Z_2]$$

Here v_1 and v_2 are weights representing the importance of Z_1 and Z_2.

The aim is to find the design that minimizes the variance of $g(\hat{\theta})$ were $g(\theta) := \underset{x>0}{argmax} \text{E}[\text{CUI}(x)]$

c-optimal Designs for the bivariate Emax model

It is straightforward to show that if a positive dose, x, exists that maximizes E[CUI(x)] then

$$g(\theta) := \underset{x>0}{argmax}\,\mathrm{E}[\mathrm{CUI}(x)] = \frac{\sqrt{v_1 ED_{50} E_{max} v_2 SD_{50} S_{max}}(ED_{50} - SD_{50}) - ED_{50} SD_{50}(v_1 E_{max} - v_2 S_{max})}{v_1 ED_{50} E_{max} - v_2 SD_{50} S_{max}}. \tag{3}$$

c-optimal Designs for the bivariate Emax model

Example

Let $E_{max} = S_{max} = 1$, $\sigma_1^2 = \sigma_2^2$, $v_1 = v_2$ and $\rho = 0$ then, for the bivariate Emax model,

(i) $\xi^* = \left\{ \begin{array}{c} \sqrt{ED_{50} SD_{50}} \\ 1 \end{array} \right\}$ is locally c-optimal when $\frac{SD_{50}}{ED_{50}} \in \left]1, \frac{5+\sqrt{21}}{2}\right]$.

(ii) $\xi^* = \left\{ \begin{array}{cc} ED_{50} & SD_{50} \\ 0.5 & 0.5 \end{array} \right\}$ is locally c-optimal when $\frac{SD_{50}}{ED_{50}} \to \infty$.

c-optimal Designs for the bivariate Emax model

Theorem

Assume that $\xi = \{x_1, \ldots, x_n; w_1, \ldots, w_n\}$ *is locally c-optimal for the Bivariate Emax model with parameters* $\theta = (ED_{50}, E_{max}, SD_{50}, S_{max})$, $v = (v_1, v_2)$ *and* $\Omega = (\sigma_1, \sigma_2, \rho)$ *i.e.* ξ *minimizes* $\Psi = \nabla g^T M^{-1} \nabla g$. *If* $a, b, c, d \in \mathbf{R} \backslash \{0\}$ *then*

1. ξ *is locally c-optimal for the same model but with one or more of the following changes for the parameters*

   (i) $v = (av_1, av_2)$
   (ii) $\Omega = (b\sigma_1, b\sigma_2, \rho)$
   (iii) $\theta = (ED_{50}, cE_{max}, SD_{50}, cS_{max})$

2. $\xi^* = \{dx_1, \ldots, dx_n; w_1, \ldots, w_n\}$ *is locally c-optimal for the same model but with*

   (iv) $\theta = (dED_{50}, E_{max}, dSD_{50}, S_{max})$.

[Note that by c-optimal we mean with respect to the function $g(\theta)$ *that maximizes the CUI.]*

Table: Locally c-optimal designs $\xi = \{x_1, x_2; w_1, 1 - w_1\}$ for the bivariate Emax model with respect to $g(\theta)$. Here $\chi = [0, \infty]$, $ED_{50} = 1$, $v_1 = v_2$, $E_{max} = S_{max} = 1$ and $\sigma_1^2 = \sigma_2^2$. If the design point x_2 is not specified then x_1 is the only design point.

SD_{50}		ρ						
		-0.9	-0.5	-0.1	0	0.1	0.5	0.9
6	x_1	$\sqrt{6}$	$\sqrt{6}$	$\sqrt{6}$	$\sqrt{6}$	$\sqrt{6}$	0.9863	0.6214
	w_1	1	1	1	1	1	0.5	0.5
	x_2						6.0832	9.6552
7	x_1	$\sqrt{7}$	$\sqrt{7}$	$\sqrt{7}$	2.1308	1.6109	0.9349	0.6412
	w_1	1	1	1	0.5	0.5	0.5	0.5
	x_2				3.2851	4.3455	7.4876	10.9169
8	x_1	$\sqrt{8}$	$\sqrt{8}$	1.9212	1.5879	1.3763	0.9093	0.6594
	w_1	1	1	0.5	0.5	0.5	0.5	0.5
	x_2			4.1640	5.0382	5.8126	8.7978	12.1318
9	x_1	$\sqrt{9}$	$\sqrt{9}$	1.5933	1.4071	1.2641	0.8958	0.6760
	w_1	1	1	0.5	0.5	0.5	0.5	0.5
	x_2			5.6488	6.3960	7.1199	10.0473	13.3137
10	x_1	$\sqrt{10}$	$\sqrt{10}$	1.4420	1.3077	1.1972	0.8885	0.6910
	w_1	1	1	0.5	0.5	0.5	0.5	0.5
	x_2			6.9346	7.6467	8.3530	11.2543	14.4707

Table: Locally c-optimal designs $\xi = \{x_1, x_2, 500; w_1, w_2, 1 - w_1 - w_2\}$ for the Bivariate Emax model with respect to $g(\theta)$. Here $\chi = [0, 500]$, $ED_{50} = 1$, $v_1 = v_2$ and $E_{max} = S_{max}$. If the design point x_2 is not specified then x_1 and 500 are the only design points.

SD_{50}		ρ ($\frac{\sigma_2^2}{\sigma_1^2} = 1$)				$\frac{\sigma_2^2}{\sigma_1^2}$ ($\rho = 0$)		
		-0.5	0	0.5	0.9	0.5	1.5	3
2	x_1	1.0793	1.1078	1.0972	0.4985	0.8437	1.3875	2.1699
	w_1	0.2800	0.3944	0.5118	0.4883	0.3702	0.4160	0.4670
	x_2				4.9811			
	w_2				0.3639			
3	x_1	1.2704	1.2833	0.8407	0.4626	0.9356	1.6057	1.7091
	w_1	0.3723	0.4903	0.4736	0.5111	0.4555	0.5197	0.3929
	x_2			6.0010	5.6854			6.3070
	w_2			0.2220	0.4213			0.2684
4	x_1	1.4553	1.1358	0.7026	0.4815	1.0312	1.1128	1.0766
	w_1	0.4188	0.4582	0.4704	0.5197	0.4956	0.4124	0.3433
	x_2		6.5538	7.6651	6.3468		7.2480	8.9210
	w_2		0.1282	0.3411	0.4305		0.2700	0.5557
5	x_1	1.3371	0.9347	0.6662	0.5040	0.9375	0.9327	0.9287
	w_1	0.3933	0.4353	0.4767	0.5232	0.4831	0.4016	0.3420
	x_2	7.2388	8.7514	8.6498	7.0101	8.5842	8.8849	9.1612
	w_2	0.0889	0.2548	0.3853	0.4343	0.0786	0.3833	0.6213

c-optimal Designs for the bivariate Emax model

- Two design points are sufficient as long as $1 < SD_{50}/ED_{50} < c$ where c is some constant. Else, if $SD_{50}/ED_{50} > c$ then an additional design point is needed.

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- The larger ρ and σ_2^2/σ_1^2 become the smaller is c for which the statement above holds.
- A study where the two responses are negatively correlated (for a fixed dose) needs, in this setting, equal or less design points than if the two responses were positively correlated.

Thanks for your attention!

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Theorem

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

$$tr(M(\xi)^{-1}M(\xi_x)) \quad \leq \quad p, \qquad \forall \ x \in \chi. \tag{4}$$

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

Theorem

(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,*

$$\nabla g^T M(\xi)^{-1} M(\xi_x) M(\xi)^{-1} \nabla g \quad \leq \quad \nabla g^T M(\xi)^{-1} \nabla g, \quad \forall \ x \in \chi. \tag{5}$$

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