# Optimal designs for dose finding studies

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Joint work with

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# Contents

## Motivating Example (anti-anxiety drug)

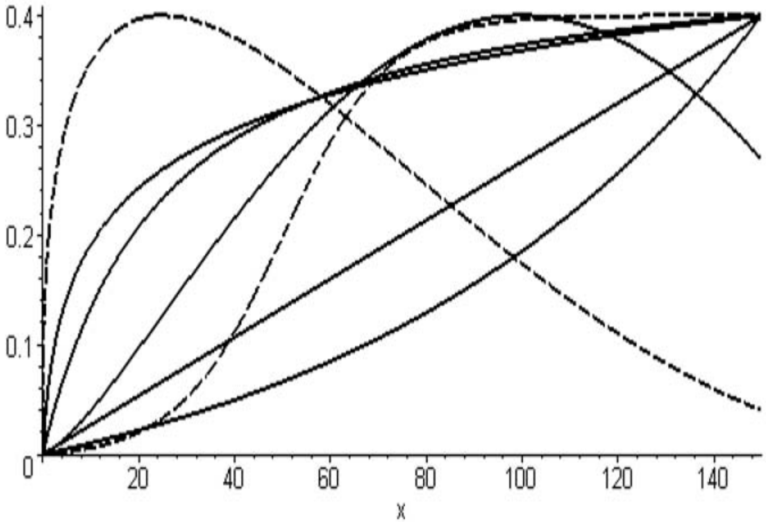
- Confirmatory trial to determine the appropriate target dose
  - Dose range $[\underline{x}, \overline{x}] = [0mg, 150mg]$ (all dose levels within this range are safe)
  - Maximum treatment effect $f_{\max} = 0.4$
- Main goal: estimation of the minimum effective dose level (target dose), which produces at least the clinically relevant effect of $\Delta = 0.2$
- A class of potential models is available (based on experience of the clinical team)

- In confirmatory trials there is usually some prior information available

- Candidate models with estimates taken from previous studies

| Model | $f(x,\vartheta)$ |
|---|---|
| linear | $(0.4/150)x$ |
| $E_{\max}$ | $(7/15)x/(25+x)$ |
| exponential | $0.08265(\exp(x/85)-1)$ |
| log-linear | $0.0797\log(x+1)$ |
| logistic | $-0.004041+0.404082/\{1+\exp((50-x)/10.88111)\}$ |
| $\text{beta}_1$ | $1.082(x/200)^{0.33}(1-x/200)^{2.31}$ |
| $\text{beta}_2$ | $2.747(x/200)^{1.39}(1-x/200)^{1.39}$ |

- All model have been normalized (maximum $= 0.4$)




- Goal: determination of target dose level
  - too high → unacceptable toxicity
  - too low → smaller chance of showing efficacy

**Problem:** efficient design of experiment for estimation of the target dose

- How do we measure the quality of a design (optimality criterion)?
- Robustness with respect to prior estimates?
- Robustness with respect to model assumptions (specification of a dose response profile)?

## Mathematical model

$$E[Y_{ij} \mid x_i] = \vartheta_0 + \vartheta_1 f^0(x_i, \vartheta^0),\ i = 1, \ldots, k,\ j = 1, \ldots, n_i,$$

- $x_1 < x_2 < \ldots < x_k$ : different dose levels
- $n_i$: number of patients treated with dose level $x_i$, $i = 1, \ldots, k$.
- $\vartheta^0 = (\vartheta_2, \ldots, \vartheta_p)^T$
- $f(x, \vartheta) = \vartheta_0 + \vartheta_1 f^0(x, \vartheta^0)$
- $\vartheta = (\vartheta_0, \vartheta_1, \vartheta_2, \ldots, \vartheta_p)^T$ ($p + 1$ parameters)

# Minimum effective dose (MED)

$$\mathrm{MED} = \inf\{x \in (\underline{x}, \overline{x}] \mid f(\underline{x}, \vartheta) < f(x, \vartheta) - \Delta\}$$

## Estimate of MED:

$$\widehat{\mathrm{MED}}_2 = \inf\{x \in (\underline{x}, \overline{x}] \mid f(\underline{x}, \hat{\vartheta}) < f(x, \hat{\vartheta}) - \Delta\,;\; L_x > f(\underline{x}, \hat{\vartheta})\}$$

- $\hat{\vartheta}$ estimate of $\vartheta$ (e.g. maximum likelihood)
- $L_x$: lower bound of the confidence interval for

$$f(x, \vartheta) = \vartheta_0 + \vartheta_1 f^0(x_i, \vartheta^0)$$

## Approximate designs I:

- Design: probability measure $\xi$ with weights $w_1, \ldots, w_k$ at dose levels $x_1 < x_2 < \ldots < x_k$

- Total sample size $n$: $\Rightarrow$ Rounding of $nw_i$ to integers such that $\sum_{i=1}^k n_i = n$, e.g. $n = 40$

$$\xi = \begin{pmatrix} 10 & 75 & 140 \\ \frac{1}{3} & \frac{1}{3} & \frac{1}{3} \end{pmatrix}$$

$$\Rightarrow \quad n_1 = 13,\ n_2 = 14,\ n_3 = 13$$

- An optimal design minimizes $\mathrm{Var}(\widehat{\mathrm{MED}}_2)$

# Approximate designs II:

- First order approximation (standard asymptotic theory):

$$\mathrm{Var}(\widehat{\mathrm{MED}_2}) \approx \frac{1}{n} b^T(\vartheta_0, \ldots, \vartheta_p) M^-(\xi, \vartheta) b(\vartheta_0, \ldots, \vartheta_p),$$

where

$$\begin{aligned} b(\vartheta) &= \frac{\partial}{\partial \vartheta} (f^0)^{-1} (f^0(\underline{x}, \vartheta^0) + \frac{\Delta}{\vartheta_1}) \\ M(\xi, \vartheta) &= \sum_{j=1}^{k} w_j \sigma^2(x_j) g(x_j, \vartheta) g^T(x_j, \vartheta) \in \mathbb{R}^{p+1 \times p+1} \\ g(x, \vartheta) &= \frac{\partial}{\partial \vartheta} f(x, \vartheta) \end{aligned}$$

- A local MED-optimal design $\xi^*(\vartheta)$ minimizes

$$\Psi(\xi) = b^T(\vartheta_0, \ldots, \vartheta_p) M^-(\xi, \vartheta) b(\vartheta_0, \ldots, \vartheta_p)$$

with respect to the design $\xi$

## Local MED-optimal designs under a given response profile:

- For the following models results are available:

| | |
|---|---|
| $f(x,\vartheta) = \vartheta_0 + \vartheta_1 x$ | linear |
| $f(x,\vartheta) = \vartheta_0 + \frac{\vartheta_1 x}{x+\vartheta_2}$ | $E_{\max}$ |
| $f(x,\vartheta) = \vartheta_0 + \vartheta_1 \exp(x/\vartheta_2)$ | exponential |
| $f(x,\vartheta) = \vartheta_0 + \vartheta_1 \log(x+\vartheta_2)$ | log-linear |
| $f(x,\vartheta) = \vartheta_0 + \vartheta_1 (1+\exp((\vartheta_2 - x)/\vartheta_3))^{-1}$ | logistic |
| $f(x,\vartheta) = \vartheta_0 + \vartheta_1 B(\vartheta_2,\vartheta_3)(x/\vartheta_4)^{\vartheta_2}(1-x/\vartheta_4)^{\vartheta_3}$ | beta |

where $B(\vartheta_2,\vartheta_3) = (\vartheta_2/(\vartheta_2+\vartheta_3))^{-\vartheta_2}(\vartheta_3/(\vartheta_2+\vartheta_3))^{-\vartheta_3}$.

- In confirmatory trials the application of local optimal designs is often justified (see the motivating example)

# Local MED-optimal designs for the EMAX model:

Define $\Delta^* = \vartheta_1\vartheta_2(\overline{x} - \underline{x})/\{2(\underline{x} + \vartheta_2)(\overline{x} + \vartheta_2)\}$.

- If $\Delta > \Delta^* \Rightarrow$ local MED-optimal design has equal weights at placebo $x_1 = \underline{x}$ and the dose level

$$x_2 = \frac{\vartheta_2(\Delta/\vartheta_1\vartheta_2 + (\Delta/\vartheta_1 + 1)\underline{x})}{\vartheta_2 - \Delta/\vartheta_1(\underline{x} + \vartheta_2)}.$$

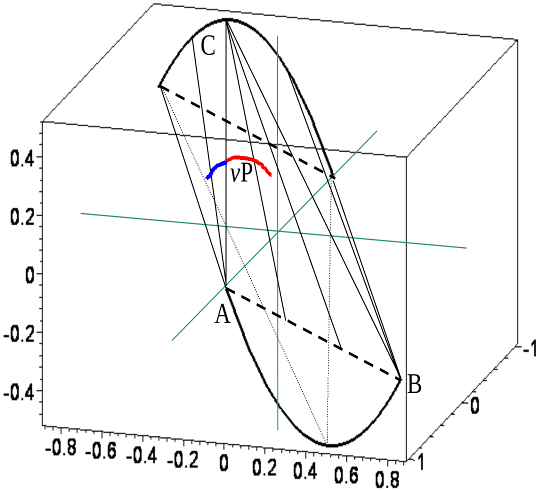
- If $\Delta < \Delta^* \Rightarrow$ local MED-optimal design has weights $w, 0.5 - w$ and 0.5 at placebo $x_1 = \underline{x}$, the maximum dose level $x_3 = \bar{x}$ and at dose level

$$x_2 = \frac{\overline{x}(\underline{x} + \vartheta_2) + \underline{x}(\overline{x} + \vartheta_2)}{(\underline{x} + \vartheta_2) + (\overline{x} + \vartheta_2)},$$

where

$$w = \frac{1}{4} - \frac{1}{8}\frac{(\overline{x} - \underline{x})\vartheta_2}{(\underline{x} - \overline{x})\vartheta_2 + (\underline{x} + \overline{x})\vartheta_2\Delta/\vartheta_1 + (\underline{x}\overline{x} + \vartheta_2^2)\Delta/\vartheta_1}.$$

# Geometric Proof (Elfving, 1952):




Elfving set

$$\mathcal{R} = \mathrm{conv}(\mathcal{X} \cup -\mathcal{X})$$

where

$$\mathcal{X} = \left\{ (1, f^0(x,\vartheta), \vartheta_1 \frac{\partial}{\partial \vartheta_2} f^0(x,\vartheta))^T \;\middle|\; x \in [0,150] \right\}$$

$$P = b(\vartheta) = \frac{\partial}{\partial \vartheta} (f^0)^{-1} (f^0(\underline{x}, \vartheta^0) + \frac{\Delta}{\vartheta_1})$$

# Numerical Results:

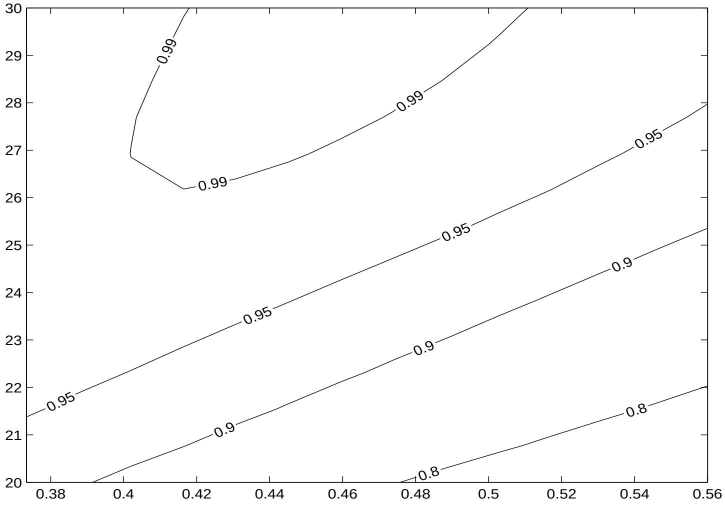
Table 1: *Local MED-optimal designs for the $E_{\max}$ model for various parameters. The dose range is the interval $[0mg, 150mg]$. The table also shows the efficiency of the standard design $\xi_s$.*

| $\Delta$ | $\vartheta_1$ | $\vartheta_2$ | $x_1$ | $x_2$ | $x_3$ | $w_1$ | $w_2$ | $w_3$ | eff($\xi_s$) |
|---|---|---|---|---|---|---|---|---|---|
| 0.2 | 0.4667 | 15 | 0 | 11.25 | | 0.5 | 0.5 | | 0.4714 |
| 0.2 | 0.4667 | 25 | 0 | 18.75 | | 0.5 | 0.5 | | 0.4545 |
| 0.2 | 0.4667 | 35 | 0 | 26.25 | | 0.5 | 0.5 | | 0.4400 |
| 0.1 | 0.4667 | 25 | 0 | 18.75 | 150 | 0.417 | 0.5 | 0.083 | 0.5341 |
| 0.3 | 0.4667 | 25 | 0 | 45.00 | | 0.5 | 0.5 | | 0.4595 |
| 0.2 | 0.2667 | 25 | 0 | 74.96 | | 0.5 | 0.5 | | 0.5078 |
| 0.2 | 0.6667 | 25 | 0 | 18.75 | 150 | 0.442 | 0.5 | 0.058 | 0.5099 |

- standard design $\xi_s$: six dose levels $0, 10, 25, 50, 100,$ and $150mg$
- local MED-optimal design saves 50% of the observations
- asymptotic advantages can be observed for finite samples by means of a simulation study
- some robustness with respect to misspecification of the initial parameters can be observed

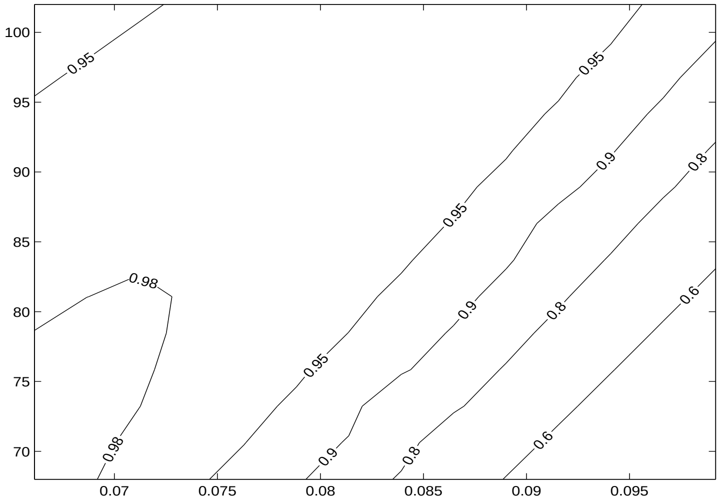
# Robustness with respect to misspecification of parameters

EMAX-model



# Robustness with respect to misspecification of parameters

Exponential-model



# Further robustness issue - the dose response surface

- what is the efficiency of the local optimal design if the dose response profile has been misspecified ?

Table 2: *Robustness of local MED-optimal designs under model misspecification*

| Model | $\xi_{[LIN]}$ | $\xi_{[E_{\max}]}$ | $\xi_{[EXP]}$ | $\xi_{[LOG]}$ | $\xi_{[logistic]}$ | $\xi_{[\text{beta}_1]}$ | $\xi_{[\text{beta}_2]}$ | $\xi_s$ |
|---|---|---|---|---|---|---|---|---|
| linear | 1.00 | 0.10 | 0.50 | 0.09 | 0.17 | 0.10 | 0.13 | 0.50 |
| $E_{\max}$ | 0.04 | 1.00 | 0.01 | 0.72 | 0.17 | 0.05 | 0.44 | 0.45 |
| exponential | 0.11 | 0.10 | 1.00 | 0.07 | 0.30 | 0.06 | 0.21 | 0.43 |
| log-linear | 0.02 | 0.62 | 0.01 | 1.00 | 0.06 | 0.43 | 0.14 | 0.43 |
| logistic | 0.08 | 0.02 | 0.00 | 0.01 | 1.00 | 0.00 | 0.05 | 0.41 |
| $\text{beta}_1$ | 0.00 | 0.00 | 0.00 | 0.01 | 0.00 | 1.00 | 0.00 | 0.12 |
| $\text{beta}_2$ | 0.05 | 0.33 | 0.01 | 0.19 | 0.20 | 0.01 | 1.00 | 0.40 |

- local MED-optimal designs are NOT robust with respect to changes of the dose response profile!

## Robust designs I

- $m$ candidate models (in our example $m = 7$)

$$f_1(x, \vartheta^{(1)}), \dots, f_m(x, \vartheta^{(m)}),$$

- $\xi_j^*(\vartheta^{(j)})$: local MED-optimal design for model $j$
- Efficiency of a given design in model $j = 1, \dots, m$:

$$\text{eff}_j(\xi) = \frac{\Psi_j(\xi_j^*(\vartheta^{(j)}))}{\Psi_j(\xi, \vartheta^{(j)})}$$

- Robust design maximizes a function of the efficiencies

$$\text{eff}_1(\xi), \dots, \text{eff}_m(\xi)$$

# Robust designs II

- Bayesian approach: maximize

$$\sum_{j=1}^{m} \alpha_j \log \text{eff}_j(\xi)$$

  $(\alpha_1, \ldots, \alpha_m)$: prior distribution for different models

- maximin approach: maximize

$$\min\{\text{eff}_j(\xi) \mid j = 1, \ldots, m\}.$$

- robust designs have to be found numerically in all cases of interest

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# Robust designs III - Example

- 7 models from the motivating example
- Calculate maximin and Bayesian (uniform prior) optimal design

| | $x_1$ | $x_2$ | $x_3$ | $x_4$ | $x_5$ | $x_6$ | $w_1$ | $w_2$ | $w_3$ | $w_4$ | $w_5$ | $w_6$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| maximin | 0 | 3.4 | 16.1 | 49.6 | 112 | 150 | 0.35 | 0.05 | 0.14 | 0.18 | 0.18 | 0.10 |
| Bayes | 0 | 2.4 | 16.7 | 49.4 | 104 | 150 | 0.35 | 0.04 | 0.16 | 0.20 | 0.20 | 0.05 |
| Standard | 0 | 10 | 25 | 50 | 100 | 150 | 0.17 | 0.17 | 0.16 | 0.16 | 0.17 | 0.17 |

- efficiencies

| | linear | $E_{\max}$ | exponential | log-linear | logistic | $\text{beta}_1$ | $\text{beta}_2$ |
|---|---|---|---|---|---|---|---|
| maximin | 0.50 | 0.54 | 0.55 | 0.50 | 0.50 | 0.50 | 0.50 |
| Bayes | 0.37 | 0.57 | 0.58 | 0.50 | 0.55 | 0.53 | 0.55 |
| standard | 0.50 | 0.45 | 0.43 | 0.43 | 0.41 | 0.12 | 0.40 |

- the maximin design improves standard design in all cases
- the Bayesian design improves standard design in most cases

# Robust designs IV - example: less response profiles

- 4 models from the motivating example (only increasing and concave functions)
- calculate maximin and Bayesian (uniform prior) optimal design

| | $x_1$ | $x_2$ | $x_3$ | $x_4$ | $w_1$ | $w_2$ | $w_3$ | $w_4$ |
|---|---|---|---|---|---|---|---|---|
| maximin | 0 | 11.4 | 49.4 | 150 | 0.33 | 0.23 | 0.22 | 0.22 |
| Bayes | 0 | 11.2 | 49.4 | 150 | 0.34 | 0.23 | 0.24 | 0.19 |

- efficiencies

| | linear | $E_{\max}$ | log-linear | logistic |
|---|---|---|---|---|
| maximin | 0.59 | 0.59 | 0.59 | 0.59 |
| Bayes | 0.54 | 0.60 | 0.60 | 0.64 |
| standard | 0.50 | 0.45 | 0.43 | 0.41 |

- Bayesian and maximin designs improve the standard design substantially in all cases

# Robust designs V - misspecification of the parameters

- Parameters have been misspecified by $-20\%, -10\%, 0\% 10\% 20\%$

| | robust local optimal designs | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | maximin | | | | Bayesian | | | |
| | Lin | EMAX | Loglin | Log | Lin | EMAX | Loglin | Log |
| -20% | .59 | .60 | .69 | .15 | .54 | .61 | .71 | .15 |
| -15% | .59 | .59 | .66 | .19 | .54 | .60 | .67 | .19 |
| -10% | .59 | .59 | .63 | .28 | .54 | .60 | .64 | .28 |
| - 5% | .59 | .59 | .61 | .45 | .54 | .60 | .62 | .47 |
| 0% | .59 | .59 | .59 | .59 | .54 | .60 | .60 | .64 |
| 5% | .59 | .60 | .58 | .40 | .54 | .61 | .59 | .41 |
| 10% | .59 | .61 | .57 | .19 | .54 | .62 | .58 | .19 |
| 15% | .59 | .62 | .56 | .09 | .54 | .64 | .57 | .09 |
| 20% | .59 | .64 | .56 | .05 | .54 | .65 | .56 | .05 |

- Bayesian and maximin designs are robust with respect to misspecification of the parameters in the linear, EMAX and log-linear model !

# Robust designs VI: misspecification of the parameters

- Use two sets of parameters for the logistic model

| | double robust local optimal designs | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | maximin | | | | Bayesian | | | |
| | Lin | EMAX | Loglin | Log | Lin | EMAX | Loglin | Log |
| -20% | .53 | .52 | .63 | .92 | .55 | .55 | .65 | .79 |
| -15% | .53 | .52 | .60 | .87 | .55 | .54 | .62 | .73 |
| -10% | .53 | .52 | .57 | .65 | .55 | .54 | .59 | .56 |
| 0% | .53 | .53 | .53 | .62 | .55 | .55 | .55 | .57 |
| 10% | .53 | .56 | .51 | .56 | .55 | .57 | .53 | .57 |
| 15% | .53 | .58 | .50 | .53 | .55 | .59 | .52 | .57 |
| 20% | .53 | .60 | .50 | .48 | .55 | .60 | .51 | .55 |

- Modified Bayesian and maximin designs are robust with respect to misspecification of the parameters in all models !

# Conclusions

- local optimal designs for MED-estimation (more generally quantile estimation)
- I did not talk about the data (categorical or not) $\Rightarrow$ conclusions are generally valid
- local MED-optimal designs can be found explicitly for a given response profile
- local MED-optimal are not too sensitive with respect to misspecification of parameters (in most models)
- in confirmatory dose finding studies prior information is often available
- a misspecification of the response profile has a serious impact on the performance of local MED-optimal designs
- robust MED-optimal designs have been determined by a Bayesian and maximin approach, which improve standard designs substantially

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