Optimal designs for inhibition models

(with Holger Dette, Katrin Kettelhake, Tilman Möller)

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The Michaelis-Menten model is given by

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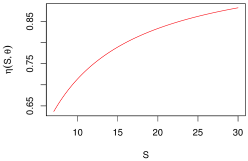

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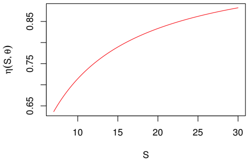
- the dose levels $S_i \in \mathcal{S} = [S_{\min}, S_{\max}]$, $0 \le S_{\min}$,
- $\tilde{\theta} = (V, K_m)^T \in \mathbb{R}^2$ is the unknown parameter,
- $\varepsilon_i \overset{i.i.d}{\sim} \mathcal{N}(0, \sigma^2)$, $\sigma^2 > 0$.



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- New drugs are often also screened for their inhibitory potential.

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BUT:

- Many diseases require co-administration of several drugs.
- New drugs are often also screened for their inhibitory potential.

➡ Adequate modeling has to reflect this fact.
➡ We extend the model by including the effect of inhibitor concentration.

The non-competitive inhibition model

Instead of the Michaelis-Menten model

$$Y_i = \eta(S_i, \tilde{\theta}) + \varepsilon_i = \frac{VS_i}{S_i + K_m} + \varepsilon_i, \quad i = 1, \ldots, n$$

where

- the dose levels $S_i \in \mathcal{S} = [S_{\text{min}}, S_{\text{max}}]$,
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The non-competitive inhibition model

We consider the non-competitive inhibition model

$$\begin{aligned} Y_i &= \eta(S_i, I_i, \theta) + \varepsilon_i \\ &= \frac{V \cdot S_i}{(K_m + S_i)(1 + \frac{I_i}{K_{ic}})} + \varepsilon_i \ , \ \ i = 1, \ldots, n, \end{aligned}$$

where

- $(S_i, I_i), \in \mathcal{S} = [S_{\min}, S_{\max}] \times [I_{\min}, I_{\max}]$,
  $0 \leq S_{\min} < S_{\max}$ and $0 \leq I_{\min} < I_{\max}$,
- $\theta = (V, K_m, K_{ic})^T \in \mathbb{R}^3$ is the unknown parameter,
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➡ GOAL: Determine optimal designs for this model.

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The structure of the information matrix

Let ξ be an approximate design with finite support in $\mathcal{S}$, that is,

$$\xi = \begin{pmatrix} (S_1, I_1) & \cdots & (S_k, I_k) \\ \xi_1 & \cdots & \xi_k \end{pmatrix}.$$

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The information matrix of the design ξ is then given by

$$M(\xi, \theta) = \int_{\mathcal{S}} \frac{\partial \eta(S, I, \theta)}{\partial \theta} \Big(\frac{\partial \eta(S, I, \theta)}{\partial \theta} \Big)^T d\xi(S, I),$$

where

$$\frac{\partial \eta(S, I, \theta)}{\partial \theta} = \frac{S}{(K_m + S)} \frac{1}{(1 + I/K_{ic})} \Big(1, -\frac{V}{K_m + S}, \frac{V \cdot I / K_{ic}^2}{1 + I/K_{ic}} \Big)^T.$$

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Considered optimality criteria

We are now interested in determining

- *D*-optimal designs, that is designs such that

$$\Phi_D\{M(\xi,\theta)\} = \det\{M(\xi,\theta)\}$$

  is maximised with respect to ξ.

Considered optimality criteria

We are now interested in determining

- D-optimal designs, that is designs such that

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is maximised with respect to ξ.

- e_j-optimal designs, $j = 1, 2, 3$, that is designs that that

$$\Phi_{e_j}\{M(\xi,\theta)\} = (e_j M^{-}(\xi,\theta) e_j)^{-1}\ , \quad j = 1, 2, 3\ .$$

is maximised with respect to ξ under the condition that $e_j \in \text{Range}(M(\xi,\theta))$.

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The non-competitive inhibition model and optimal design

Main problem:

- Model is highly non-linear and therefore the criteria are difficult to analyse mathematically.

That is the reason why:

- Not much literature on optimal designs for this type of models. (see Youdim et al. (2010); Bogacka et al. (2011); Atkinson and Bogacka (2013); Chen et al. (2017))
- Most results exist for D-optimal and D_s-optimal designs.
- In most cases optimal designs have to be found numerically.

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- In most cases optimal designs have to be found numerically.

Our idea:

- Use a non-linear transformation of the variables (S, I) to achieve multivariate polynomial regression model.

  ➡ Then the analysis of the model becomes much easier.

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Transformation of the variable (S, I)

We define a one-to-one transformation of the variable (S, I) by

$$\begin{pmatrix} x \\ y \end{pmatrix} = \psi(S, I) = \begin{pmatrix} \frac{S}{K_m + S} \\ \frac{1}{1 + I/K_{ic}} \end{pmatrix}.$$

where $(x, y) \in \mathcal{X} = [x_{\min}, x_{\max}] \times [y_{\min}, y_{\max}]$.

The boundary points of the two intervals are defined by

$$x_{\min} = \frac{S_{\min}}{K_m + S_{\min}};\ x_{\max} = \frac{S_{\max}}{K_m + S_{\max}};\ \ y_{\min} = \frac{1}{1 + I_{\max}/K_{ic}};\ \ y_{\max} = \frac{1}{1 + I_{\min}/K_{ic}}.$$

Note that $x_{\min}, x_{\max}, y_{\min}, y_{\max} \in [0, 1]$.

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Transformation of the gradient

Using the transformation the gradient

$$\frac{\partial\eta(S,I,\theta)}{\partial\theta} = \frac{S}{(K_m+S)}\frac{1}{(1+I/K_{ic})}\left(1, -\frac{V}{K_m+S}, \frac{V\cdot I/K_{ic}^2}{1+I/K_{ic}}\right)^T$$

can be represented by

$$\frac{\partial\eta(S,I,\theta)}{\partial\theta} = A(\theta)f(x,y),$$

where the non-singular matrix $A(\theta)$ and the vector $f(x,y)$ are given by

$$A(\theta) = \begin{pmatrix} 1 & 0 & 0 \\ -\frac{V}{K_m} & \frac{V}{K_m} & 0 \\ \frac{V}{K_{ic}} & 0 & -\frac{V}{K_{ic}} \end{pmatrix}, \quad f(x,y) = xy\begin{pmatrix} 1 \\ x \\ y \end{pmatrix}.$$

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The vector $f(x,y)$ corresponds to the regression function of a multivariate polynomial regression model.

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Transformation of the design and the information matrix

We transform the design ξ, that is,

$$\xi \text{ design on } \mathcal{S} \underset{\psi^{-1}(x,y)}{\overset{\psi(S,I)}{\rightleftharpoons}} \tilde{\xi} \text{ induced design on } \mathcal{X}.$$

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The information matrix can then be represented by

$$M(\xi,\theta) = A(\theta)\tilde{M}(\tilde{\xi})A^T(\theta),$$

where the matrix $\tilde{M}(\tilde{\xi})$ is defined by

$$\tilde{M}(\tilde{\xi}) = \int_{\mathcal{X}} f(x,y)f^T(x,y)d\tilde{\xi}(x,y).$$

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Transformation of the criteria

$$\text{maximising } \Phi(M(\xi,\theta)) \Leftrightarrow \text{maximising } \Phi(A(\theta)\tilde{M}(\tilde{\xi})A^T(\theta)).$$

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In the case of D-optimality, we get:

$$\Phi_D(M(\xi,\theta)) = \Phi_D(A(\theta)\tilde{M}(\tilde{\xi})A^T(\theta)) = (\det A(\theta))^2(\det \tilde{M}(\tilde{\xi})).$$

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In the case of e_j-optimality, we get for $j = 1, 2, 3$:

$$\begin{aligned}
\Phi_{e_j}(M(\xi,\theta)) &= (e_j^T(A(\theta)\tilde{M}(\tilde{\xi})A^T(\theta))^- e_j)^{-1} \\
&= ((A^{-1}(\theta)e_j)^T \tilde{M}^-(\tilde{\xi})(A^{-1}(\theta))^{-1}e_j))^{-1} \\
&= (\tilde{e}_j^T \tilde{M}^-(\tilde{\xi})\tilde{e}_j)^{-1}.
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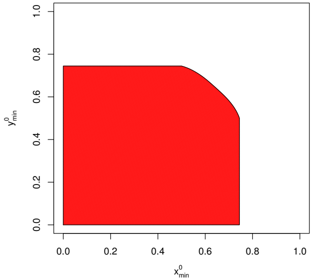
Structure of D-optimal designs I

Theorem

Let $\mathcal{X} = [x_{\min}, x_{\max}] \times [y_{\min}, y_{\max}]$ and $x^0_{\min} = \frac{x_{\min}}{x_{\max}}$, $y^0_{\min} = \frac{y_{\min}}{y_{\max}}$. The D-optimal design is supported at three points if and only if $(x^0_{\min}, y^0_{\min})$ is within the set $\mathcal{D} \subset \mathbb{R}^2$.



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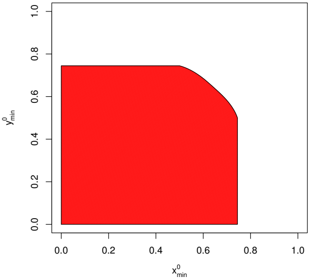
Structure of D-optimal designs II

Theorem

Let $\mathcal{X} = [x_{\min}, x_{\max}] \times [y_{\min}, y_{\max}]$ *and* $x^0_{\min} = \frac{x_{\min}}{x_{\max}}$, $y^0_{\min} = \frac{y_{\min}}{y_{\max}}$.
If $(x^0_{\min}, y^0_{\min}) \in \mathcal{D} \subset \mathbb{R}^2$, *the D-optimal design is given by*

$$\tilde{\xi}^* = \begin{pmatrix} \left(\max\{x_{\min}, \frac{x_{\max}}{2}\}, y_{\max}\right) & \left(x_{\max}, \max\{\frac{y_{\max}}{2}, y_{\min}\}\right) & (x_{\max}, y_{\max}) \\ \frac{1}{3} & \frac{1}{3} & \frac{1}{3} \end{pmatrix}.$$



Remarks to D-optimal designs

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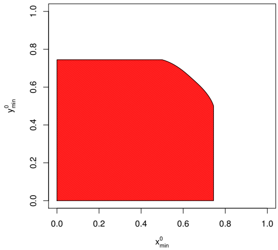
Remarks to D-optimal designs

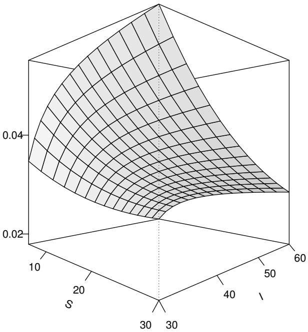
- Bogacka et al. (2011) stated that the D-optimal design is always supported by three points.
- Chen et al. (2017) found a parameter combination where the corresponding design with three support points fails to be D-optimal.
- Because of the transformation we were able to derive explicit conditions under which the saturated design is D-optimal.



Example

Let $\theta = (V, K_m, K_{ic})^T = (1, 4, 2)^T$ and $\mathcal{S} = [7, 30] \times [30, 60]$.

Then the regression function is given by $\eta(S, I, \theta) = \frac{S}{(4+S)(1+\frac{I}{2})}$.



Example (continued)

Let $\theta = (V, K_m, K_{ic})^T = (1, 4, 2)^T$ and $\mathcal{S} = [7, 30] \times [30, 60]$.

The transformed design space is then given by: $\mathcal{X} = [\frac{7}{11}, \frac{15}{17}] \times [\frac{1}{31}, \frac{1}{16}]$.

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Example (continued)

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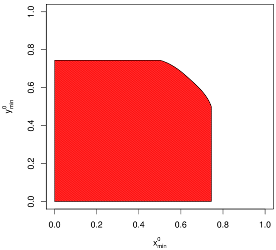
The transformed design space is then given by: $\mathcal{X} = [\frac{7}{11}, \frac{15}{17}] \times [\frac{1}{31}, \frac{1}{16}]$.

Therefore: $x^0_{\min} = \frac{119}{165}$ and $y^0_{\min} = \frac{16}{31}$ and $(x^0_{\min}, y^0_{\min}) \in \mathcal{D}$.



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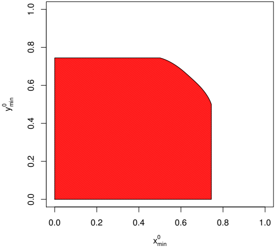
Therefore: $x^0_{\min} = \frac{119}{165}$ and $y^0_{\min} = \frac{16}{31}$ and $(x^0_{\min}, y^0_{\min}) \in \mathcal{D}$.

The D-optimal design is (using the transformation to the original space):

$$\xi^* = \begin{pmatrix} (7, 30) & (30, 30) & (30, 60) \\ \frac{1}{3} & \frac{1}{3} & \frac{1}{3} \end{pmatrix}.$$

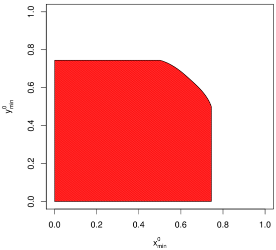


Example (continued)

Let $\theta = (V, K_m, K_{ic})^T = (1, 4, 2)^T$ and $\mathcal{S} = [15, 30] \times [30, 60]$.

The transformed design space is then given by: $\mathcal{X} = [\frac{15}{19}, \frac{15}{17}] \times [\frac{1}{31}, \frac{1}{16}]$.

Therefore: $x^0_{\text{min}} = \frac{17}{19}$ and $y^0_{\text{min}} = \frac{16}{31}$ and $(x^0_{\text{min}}, y^0_{\text{min}}) \notin \mathcal{D}$.



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e_j-optimality in the transformed model

In the case of e_j-optimality, we get for $j = 1, 2, 3$:

$$\begin{aligned} \Phi_{e_j}(M(\xi,\theta)) &= ((A^{-1}(\theta)e_j)^T \tilde{M}^-(\tilde{\xi})(A^{-1}(\theta))^{-1}e_j))^{-1} \\ &= (\tilde{e}_j^T \tilde{M}^-(\tilde{\xi})\tilde{e}_j)^{-1}. \end{aligned}$$

What does $\tilde{e}_j$ look like for the different cases?

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$$\tilde{e}_j = \begin{cases} (1,1,1)^T\ , & j = 1 \\ \frac{K_m}{V} e_2\ , & j = 2 \\ \frac{K_{ic}}{V} e_3\ , & j = 3 \end{cases}.$$

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Optimal designs for $\tilde{e}_2$

Theorem

The optimal design maximising $(\tilde{e}_2^T \tilde{M}^-(\tilde{\xi})\tilde{e}_2)^{-1}$ *is of the form*

$$\tilde{\xi} = \begin{pmatrix} (x_{\max}, y_{\max}) & (\overline{x}, y_{\max}) \\ \frac{\overline{x}}{1+\overline{x}} & \frac{1}{1+\overline{x}} \end{pmatrix},$$

where $\overline{x} = \max\left\{x_{\min}, (\sqrt{2}-1)x_{\max}\right\}$.

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where $\overline{x} = \max\left\{x_{\min}, (\sqrt{2}-1)x_{\max}\right\}$.

➡ We have to transform the design $\tilde{\xi}$ to the original space $\mathcal{S}$ to get the optimal design for estimating the Michaelis-Menten constant K_m.

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Optimal design for estimating the parameter K_m

Corollary

The optimal design for estimating the Michaelis-Menten constant K_m is given by

$$\xi = \begin{pmatrix} (S_{\max}, I_{\min}) & (\overline{S}, I_{\min}) \\ 1-\omega & \omega \end{pmatrix},$$

where

$$\begin{aligned} \overline{S} &= \max\left\{ S_{\min} \, , \, \frac{K_m S_{\max}(\sqrt{2}-1)}{K_m + (2-\sqrt{2})S_{\max}} \right\}, \\ \omega &= \left(1 + \max\left\{ \frac{S_{\min}}{K_m + S_{\min}} \, , \, \frac{(\sqrt{2}-1)S_{\max}}{K_m + S_{\max}} \right\} \right)^{-1}. \end{aligned}$$

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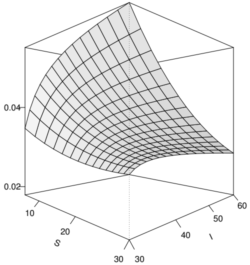
Example(continued)

Let $\theta = (V, K_m, K_{ic})^T = (1, 4, 2)^T$ and $\mathcal{S} = [7, 30] \times [30, 60]$.

Then the design for estimating the constant K_m is given by

$$\xi = \begin{pmatrix} (7,30) & (30,30) \\ 0.6\bar{1} & 1-0.6\bar{1} \end{pmatrix}.$$



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Conclusion and further comments

- The non-linear transformation is useful to make the optimisation problem more tractable.
- Similar transformations are possible for other inhibition models and can simplify the (numerical) optimisation problem.
- For instance, we can use the algorithm presented by Fabrice Gamboa today.

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Thank you very much for your attention!

References

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