About c- and D-optimal dose-finding designs for bivariate outcomes

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Efficacy-safety-models

- Risk-benefit consideration often important for dose-finding

➢ Consider both an efficacy and safety outcome for planning the design

- For patient $i, i = 1, \ldots, n,$ we observe:

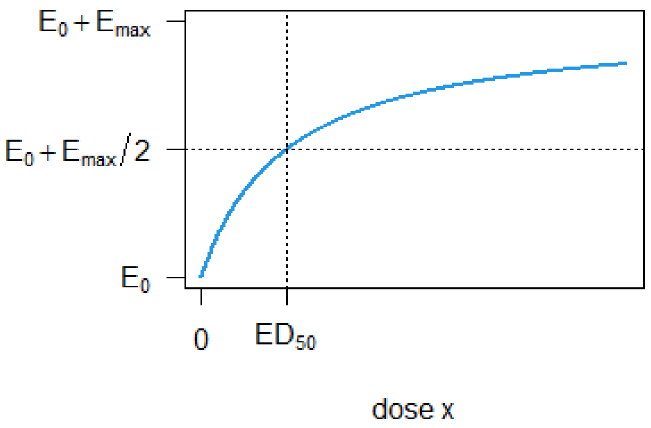
$$\binom{Y_{Ei}}{Y_{Si}} = \binom{f(\boldsymbol{\theta_E}, x_i)}{f(\boldsymbol{\theta_S}, x_i)} + \binom{\epsilon_{Ei}}{\epsilon_{Si}}$$

with regression function f depending on dose x_i;

$$(\epsilon_{Ei}, \epsilon_{Si})^{\mathrm{T}} \sim N(0, \boldsymbol{\Sigma}), \qquad Corr(\epsilon_{Ei}, \epsilon_{Si}) = \rho$$

Efficacy-safety-models

- **Emax-Smax**-model: $f(\boldsymbol{\theta}, x) = \theta_1 + \frac{\theta_3 x}{x+\theta_2}$,
  $\boldsymbol{\theta}_E = (E_0, ED_{50}, E_{max})$, $\boldsymbol{\theta}_S = (S_0, SD_{50}, S_{max})$



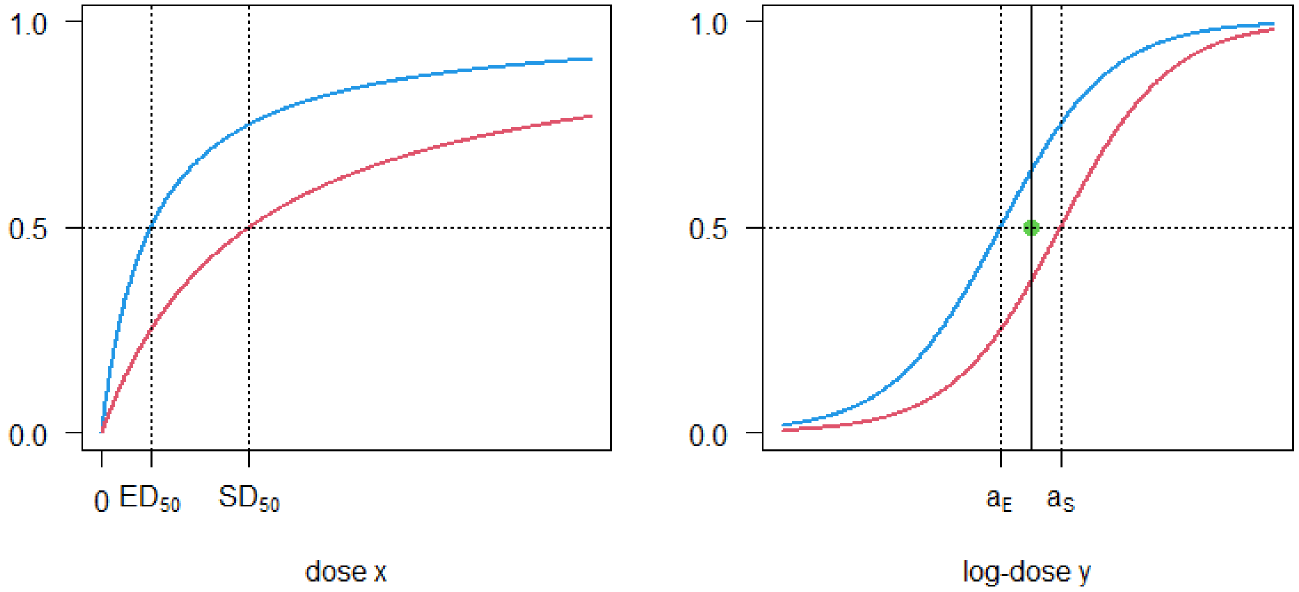
- Further models of Emax-type:
  - **Michaelis-Menten** model: $E_0 = S_0 = 0$
  - **Placebo-effect** model: $E_{max} = S_{max} = 1$
  - **One-parameter** model: $E_0 = S_0 = 0$, $E_{max} = S_{max} = 1$, i.e.
    $f(ED_{50}, x) = x/(x + ED_{50})$, $f(SD_{50}, x) = x/(x + SD_{50})$

Optimal design

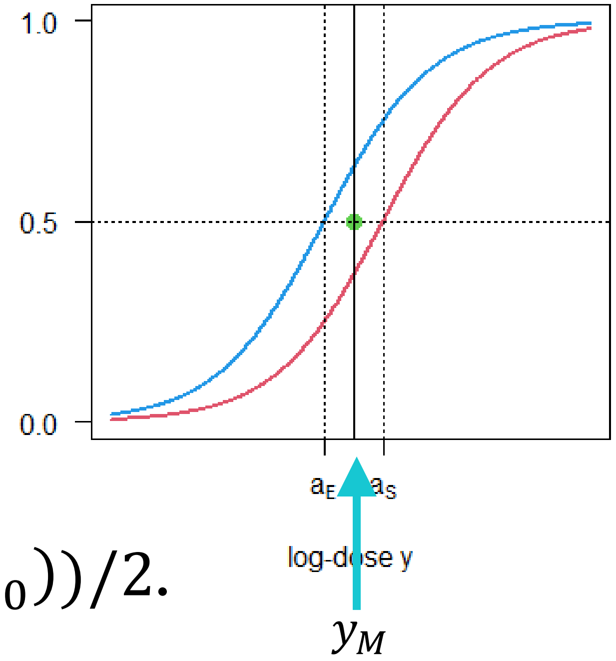
- Design
$$\xi = \begin{pmatrix} x_1 & x_2 & \dots & x_n \\ w_1 & w_2 & \dots & w_n \end{pmatrix}$$
with doses $x_i \in [0, \infty]$ (unrestricted design space); $w_i > 0$, $\sum_{i=1}^{n} w_i = 1$
- Optimize standardized information matrix
$$\boldsymbol{M}(\xi) = \sum_{i=1}^{n} w_i \, \boldsymbol{M}\left(\xi_{x_i}\right)$$
with
$$\boldsymbol{M}(\xi_x) = \left(\frac{\partial \boldsymbol{h}(x)}{\partial \boldsymbol{\theta}}\right)^T \boldsymbol{\Sigma}^{-1} \left(\frac{\partial \boldsymbol{h}(x)}{\partial \boldsymbol{\theta}}\right)$$
$\boldsymbol{\theta} = (\boldsymbol{\theta}_E, \boldsymbol{\theta}_S)$,
$\boldsymbol{h}(\boldsymbol{\theta}, x) = (f(\boldsymbol{\theta}_E, x), f(\boldsymbol{\theta}_S, x))$
- We are interested in locally D- and c-optimal designs

Log-transformation of dose-scale

- $f(\boldsymbol{\theta_E}, x) = E_0 + \frac{E_{max} x}{x + ED_{50}}$, $f(\boldsymbol{\theta_S}, x) = S_0 + \frac{S_{max} x}{x + SD_{50}}$
- Log-transform: $y = \log(x)$ and $a_E = \log(ED_{50})$, $a_S = \log(SD_{50})$
- $\tilde{f}(\theta_E, y) = E_0 + \frac{E_{max}}{1 + \exp(-y + a_E)}$, $\tilde{f}(\boldsymbol{\theta_S}, y) = S_0 + \frac{S_{max}}{1 + \exp(-y + a_S)}$



Symmetric designs



Theorem:
Unrestricted design space $[-\infty, \infty]$ on log-scale;
model: one-parameter, placebo effect, or Emax-Smax.

There is a D-optimal design which is symmetric around
$y_M = \log(\sqrt{ED_{50}SD_{50}}) = \frac{a_E + a_S}{2} = (\log(ED_{50}) + \log(SD_{50}))/2.$

Result valid also for c-optimality with **c** for inference on $a_E + a_S$ or $a_S - a_E$
($a_S - a_E$ corresponds to the therapeutic index of a drug: $TI = \frac{SD_{50}}{ED_{50}} (\geq 1)$)

The one-parameter model

$f(ED_{50}, x) = \frac{x}{x+ED_{50}}$,
$f(SD_{50}, x) = \frac{x}{x+SD_{50}}$,
$TI = \frac{SD_{50}}{ED_{50}}$

Theorem (Tsirpitzi & Miller, 2021): Let $\boldsymbol{c} = \begin{pmatrix} 1 \\ 1 \end{pmatrix}$, $\boldsymbol{\Sigma} = \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix}$:

- If $TI \leq 4/\left(-\rho + 3 - \sqrt{\rho^2 - 6\rho + 5}\right)^2$, the one-point design in $x_M = \exp(y_M) = \sqrt{ED_{50} SD_{50}}$ is **c**-optimal,
- Otherwise, following two-point design is **c**-optimal:
  $\begin{pmatrix} \exp(y_M - \delta) & \exp(y_M + \delta) \\ 1/2 & 1/2 \end{pmatrix}$;
  an algebraic expression for $\delta > 0$ is given by Tsirpitzi & Miller (2021)

The Emax-Smax model

$$f(\boldsymbol{\theta_E}, x) = E_0 + \frac{E_{max}x}{x + ED_{50}},$$
$$f(\boldsymbol{\theta_S}, x) = S_0 + \frac{S_{max}x}{x + SD_{50}}$$
$$TI = \frac{SD_{50}}{ED_{50}}$$

Theorem:

- For $TI = \frac{SD_{50}}{ED_{50}} > 1$ close to 1, a 3-point design is D-optimal:

  $$\begin{pmatrix} 0 & x_M & \infty \\ 1/3 & 1/3 & 1/3 \end{pmatrix} \text{with } x_M = \exp(y_M) = \sqrt{ED_{50}SD_{50}}$$

- For larger TI, the D-optimal design is a 4-point design and has the form

  $$\begin{pmatrix} 0 & \exp(y_M - \delta) & \exp(y_M + \delta) & \infty \\ \frac{1}{2} - w & w & w & \frac{1}{2} - w \end{pmatrix}$$

  with some $w \in (0, 1/2), \delta \geq 0$

Restricted design spaces with left or right limits

- Unrestricted design space [0, ∞] is a theoretical construct
- For the Emax-Smax model, we can transform a model on a restricted design space [0, R] or [L, R] to a model on an unrestricted space

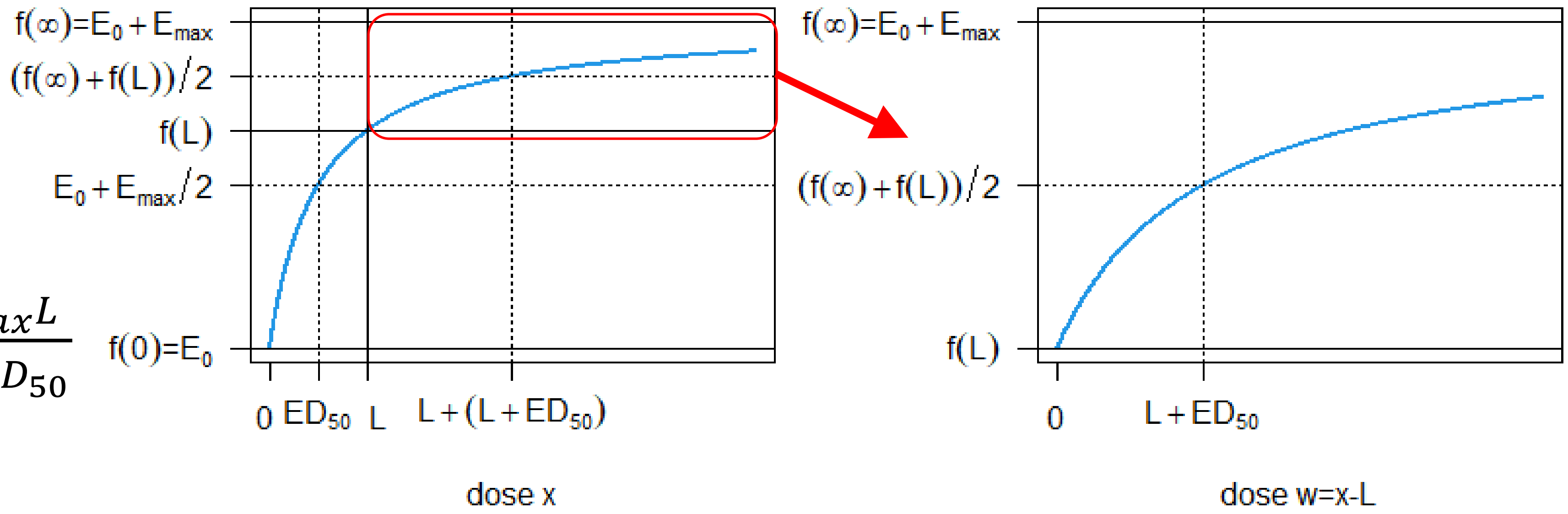
Transformation: Additive shift

- Additive shift-transformation $w = x - L$ (dose in addition to L)
- Transforms design space [L, ∞] to [0, ∞]
- We obtain a new Emax model: $f(\boldsymbol{\theta}_{\boldsymbol{E}}, x) = E_0 + \frac{E_{max}x}{x+ED_{50}} = \widetilde{E_0} + \frac{\widetilde{E_{max}}w}{w+\widetilde{ED_{50}}}$
- It has parameters

$$\widetilde{ED_{50}} = L + ED_{50},$$

$$\widetilde{E_0} = E_0 + \frac{E_{max}L}{L+ED_{50}},$$

$$\widetilde{E_{max}} = E_{max} - \frac{E_{max}L}{L+ED_{50}}$$

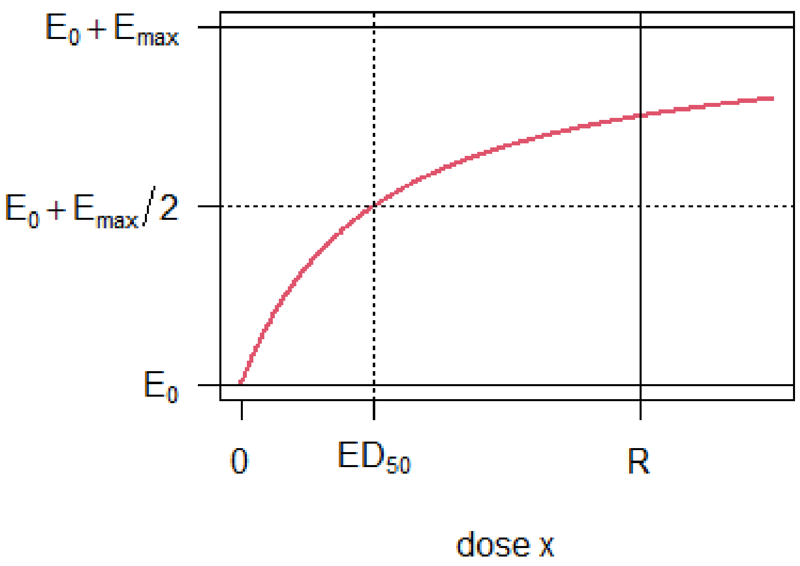


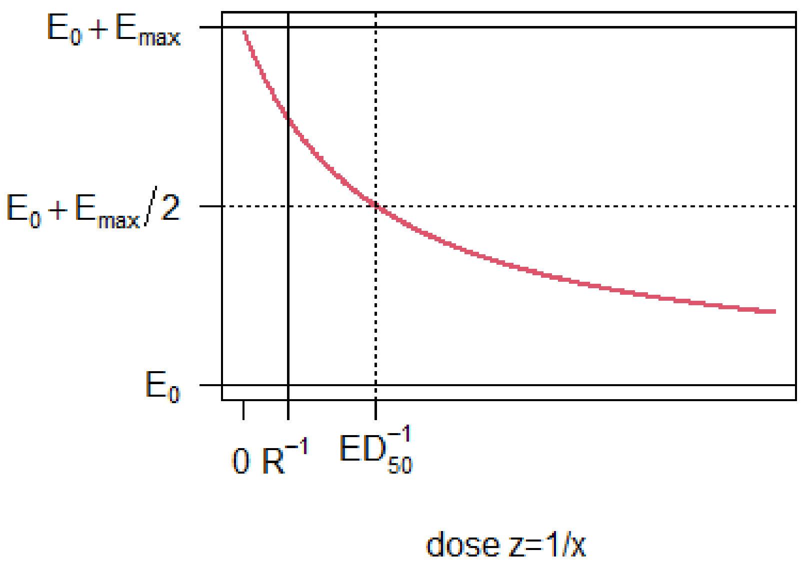
Transformation: Reciprocal

- Reciprocal transformation $z = \frac{1}{x}$
- Transforms design space $[0, R]$ to $[\frac{1}{R}, \infty]$
- We obtain a new Emax model: $E_0 + \frac{E_{max}x}{x+ED_{50}} = \widetilde{E_0} + \frac{\widetilde{E_{max}}z}{z+\widetilde{ED_{50}}}$
- It has parameters
  $\widetilde{ED_{50}} = 1/ED_{50}$,

  $\widetilde{E_0} = E_0 + E_{max}$,

  $\widetilde{E_{max}} = -E_{max}$





D-optimality for Emax-Smax model and restricted design space **[0, R]**

- D-optimal 3-point design is $\begin{pmatrix} 0 & x_M & R \\ 1/3 & 1/3 & 1/3 \end{pmatrix}$ with $x_M = \left\{ \sqrt{\left(\frac{1}{SD_{50}} + \frac{1}{R}\right)\left(\frac{1}{ED_{50}} + \frac{1}{R}\right)} + \frac{1}{R} \right\}^{-1}$

Another equivalent expression is given by Schorning et al. (2017)

- For $TI = \frac{SD_{50}}{ED_{50}} > 1$ close to 1, this 3-point design is D-optimal

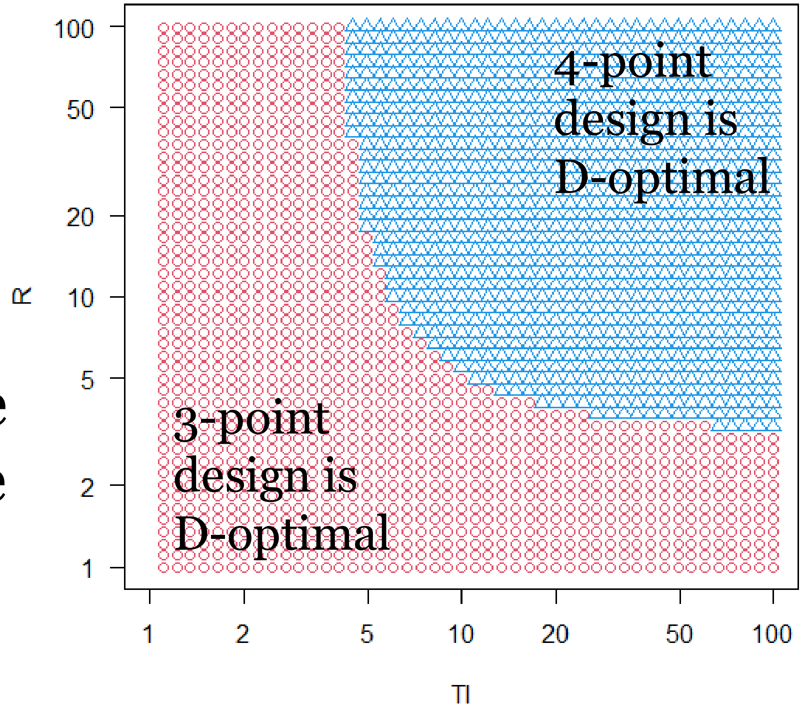
- For larger TI, $\begin{pmatrix} 0 & x_2 & x_3 & R \\ \frac{1}{2} - w & w & w & \frac{1}{2} - w \end{pmatrix}$ is D-optimal with

$$x_2 = \left\{ \sqrt{\left(\frac{1}{SD_{50}} + \frac{1}{R}\right)\left(\frac{1}{ED_{50}} + \frac{1}{R}\right)} * \psi + \frac{1}{R} \right\}^{-1}, x_3 = \left\{ \sqrt{\left(\frac{1}{SD_{50}} + \frac{1}{R}\right)\left(\frac{1}{ED_{50}} + \frac{1}{R}\right)} / \psi + \frac{1}{R} \right\}^{-1}$$

for some $w \in (0, \frac{1}{2})$ and some $\psi > 1$

D-optimality for Emax-Smax model and restricted design space **[0, R]**

- When is a design with 3 or 4 support points D-optimal?
- D-optimal: 3-point if TI or design space [0, R] small, 4-point if TI and [0, R] are larger



$(\rho = 0)$

Summary

- We could derive **algebraic results** for D- and c-optimal designs in efficacy-safety models
- Those show the **important influence parameters**
- **Transformations** for Emax-type-models are useful

References

- Schorning K, Dette H, Kettelhake K, Wong KW, Bretz F (2017). Optimal designs for active controlled dose-finding trials with efficacy-toxicity outcomes. *Biometrika*, **107**, 1003-1010.
- Tsirpitzi R, Miller F (2021). Optimal dose-finding for efficacy-safety-models. *Biometrical Journal*, **63**, 1185-1201.

Appendix

Number of support points of the optimal design

- How many support points are sufficient to ensure that we find an optimal design among them?

Model	Parameters	Arbitrary criterion	c-optimality
One-parameter	(ED_{50}, SD_{50})	4	2**
Placebo-effect	$(E_0, ED_{50}, S_0, SD_{50})$	5	4
Michaelis-Menten	$(ED_{50}, E_{max}, SD_{50}, S_{max})$	5*	4**
Emax-Smax	$(E_0, ED_{50}, E_{max}, S_0, SD_{50}, S_{max})$	5*	5*

*Schorning et al. (2017) **Tsirpitzi & Miller (2021)

Optimal design

- Design

$$\xi = \begin{pmatrix} y_1 & y_2 & \dots & y_n \\ w_1 & w_2 & \dots & w_n \end{pmatrix}$$

- Weight $w_i > 0$ for the doses $y_i \in [-\infty, \infty]$ with $\sum_{i=1}^{n} w_i = 1$
- Standardized information matrix $M(\xi) = \sum_{i=1}^{n} w_i M(\xi_{y_i})$ with

  $M\left(\xi_y\right) = Q_y^T \Sigma^{-1} Q_y,$

$$Q_y = \begin{pmatrix} 1 & h_E(y) & E_{max} d_E(y) & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & h_S(y) & S_{max} d_S(y) \end{pmatrix}$$

$$h_E(y) = \{1 + \exp(-y + a_E)\}^{-1}, d_E(y) = h_E(y)(1 - h_E(y))$$
$$h_S(y) = \{1 + \exp(-y + a_S)\}^{-1}, d_S(y) = h_S(y)(1 - h_S(y))$$

- We want to have a design ξ such that $M(\xi)$ is “large”

D-optimality for Emax-Smax model and restricted design space [0, R]

- D-optimal 3-point design is $\begin{pmatrix} 0 & x_M & R \\ 1/3 & 1/3 & 1/3 \end{pmatrix}$ with

$x_M = \frac{\sqrt{ED_{50}SD_{50}(R+ED_{50})(R+SD_{50})} - ED_{50}SD_{50}}{R+ED_{50}+SD_{50}}$ (Schorning et al., 2017)

- Note: $x_M = \left\{ \sqrt{\left(\frac{1}{SD_{50}} + \frac{1}{R}\right)\left(\frac{1}{ED_{50}} + \frac{1}{R}\right)} + \frac{1}{R} \right\}^{-1}$

Result for the placebo-effect model

- $f(\theta_E, x) = E_0 + \frac{x}{x+ED_{50}}, f(\theta_S, x) = S_0 + \frac{x}{x+SD_{50}}$
- **Theorem:**
  The D-optimal design for the design space $y \in [-\infty, \infty)$ has the form

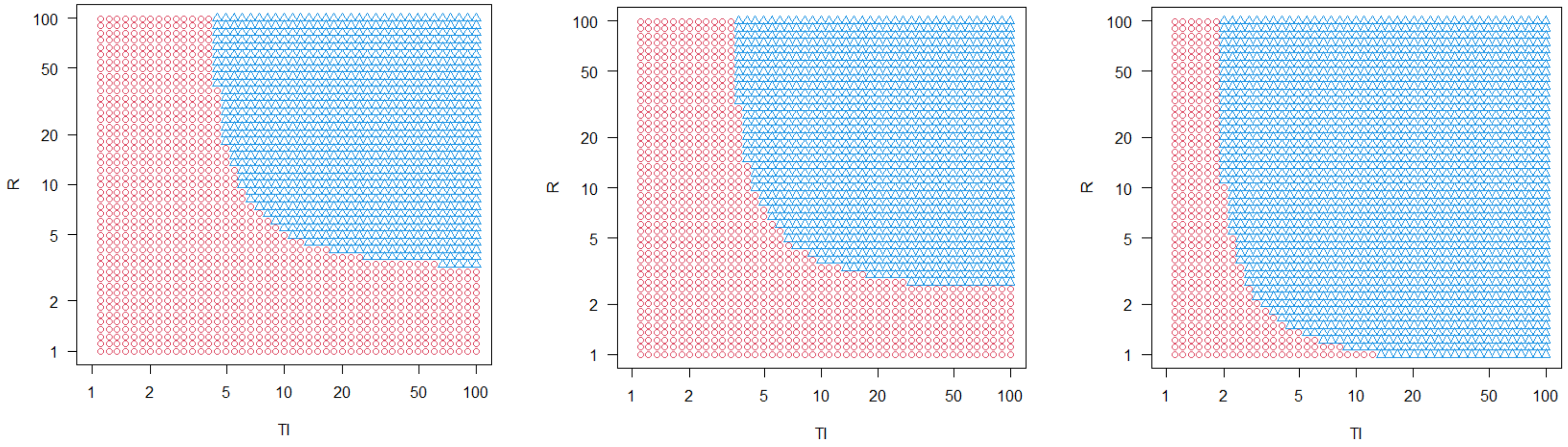
$$\begin{pmatrix} -\infty & \exp(y_S - \delta) & \exp(y_S + \delta) \\ 1 - 2w & w & w \end{pmatrix}$$

  with $y_S = \log\left(\sqrt{ED_{50} SD_{50}}\right)$ and some $w \in \left(0, \frac{1}{2}\right), \delta \geq 0$.

D-optimality for Emax-Smax model and restricted design space [0, R]

- When is a design with 3 or 4 support points D-optimal?

rho=0 rho=0.5 rho=0.9



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Michaelis-Menten	$(ED_{50}, E_{max}, SD_{50}, S_{max})$	5^{*}	4^{**}
Emax-Smax	$(E_0, ED_{50}, E_{max}, S_0, SD_{50}, S_{max})$	5^{*}	5^{*}

*Schorning et al. (2017) **Tsirpitzi & Miller (2021)

- Optimal designs depend not on $E_0, S_0, E_{max}, S_{max}$ but on ED_{50}, SD_{50} and ρ
- We will derive locally optimal designs which can be applied sequentially