PSI Pre-Clinical SIG

Optimal experimental design in preclinical dose-response studies

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Deutsches Krebsforschungszentrum

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14:00-15:00 BST | 15:00-16:00 CEST

OPTIMAL EXPERIMENTAL DESIGN FOR

Preclinical Dose-Response Studies for single substances and combinations

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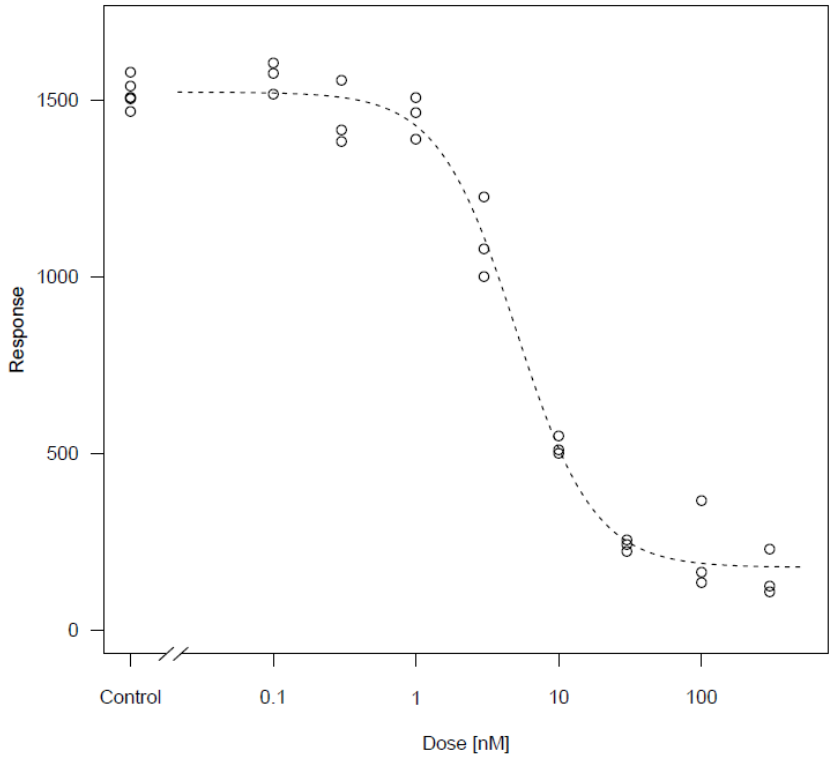
1. Motivation: Nonlinear function fits



$$f(x,d,c,b,e) = c + \frac{d-c}{1+\exp(b(\log(x)-\log(e)))}$$

Log-Logistic Funktion

2. Non-Linear Regression Models

- $Y = f(X,\beta) + \varepsilon$

  Variance of estimator for β :

  $V \approx \sigma^2 (F^T F)^{-1}$

- $F = F(X, \beta)$ is the matrix of derivatives of f regarding β.

-> Choose X (e.g. dose levels and frequencies) in a way to minimize V!

2. Non-Linear Regression Models

Minimize V-> Maximize F^TF (Information Matrix M)

$$F = \begin{pmatrix} \frac{\partial f(x_1)}{\partial b} & \cdots & \frac{\partial f(x_n)}{\partial b} \\ \frac{\partial f(x_1)}{\partial c} & \cdots & \frac{\partial f(x_n)}{\partial c} \\ \frac{\partial f(x_1)}{\partial d} & \cdots & \frac{\partial f(x_n)}{\partial d} \\ \frac{\partial f(x_1)}{\partial e} & \cdots & \frac{\partial f(x_n)}{\partial e} \end{pmatrix}$$

For a single dose level called Elementary Information Matrix

3. Statistical Optimal Design

- Matrix cannot be maximized as a whole

-> Maximize matrix function (Information Function), e.g.

- Determinant ($|F^TF|$, „average“ variance, D-Optimality)

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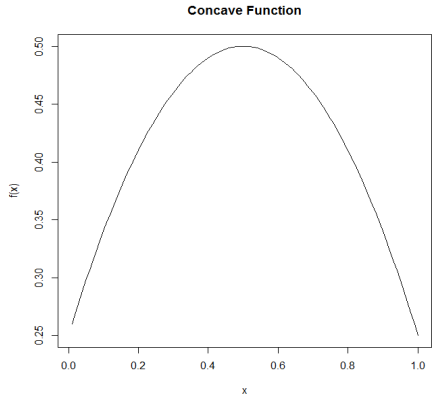
- Variance for linear combination of parameters $c^T\beta$, given by vector c
  Example: c = (0,0,0,1) will minimize variance of 4. parameter ED50
  -> minimize $c^T (F^TF)^{-1}c$ (c-Optimality)

- Other functions of parameters (ED75, MED, …) also require c-optimality

3. Statistical Optimal Design

Information functions are generally concave. This means:

- No local maxima
- Derivatives will always point in direction of global maximum
- Matrix-wise derivatives used (Frechet-derivatives)
- Derivatives can measure change from one information matrix M (existing design) in direction of all elementary information matrices
- Simple algorithmic solutions possible (Yu, 2010, Yang, 2013, ...)
- At optimum, all derivatives will be zero or less (equivalence theorem)



4. D vs. c-Optimal Designs

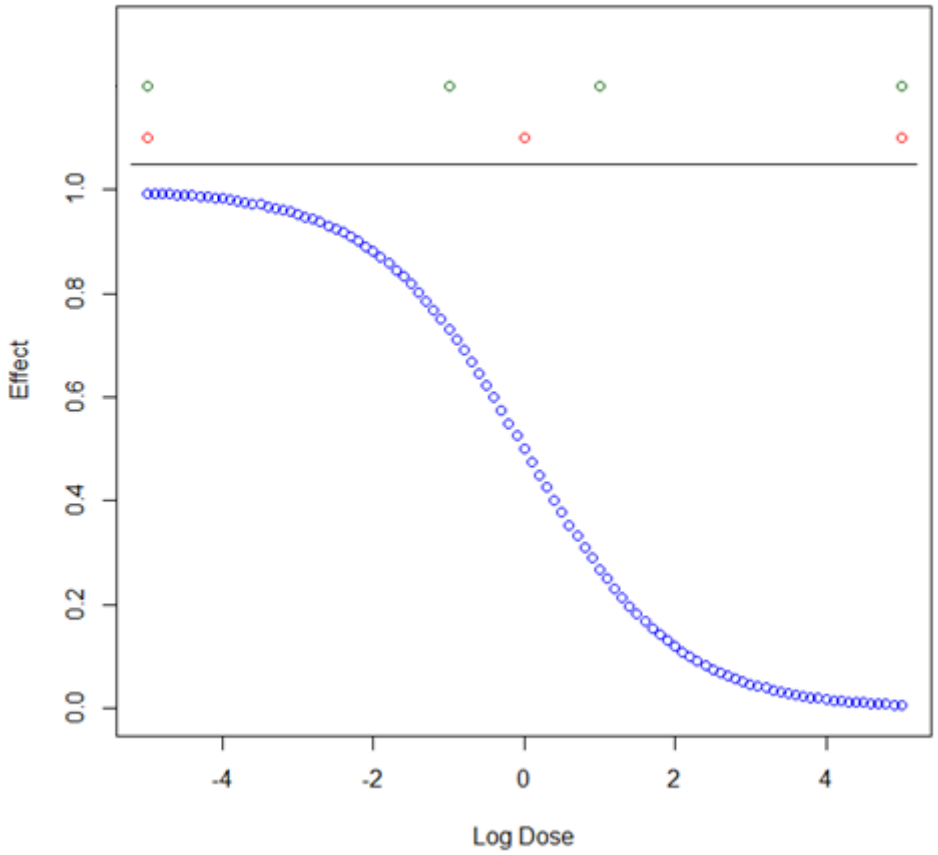
Log-logistic function (e=1, b=1)

D-Design:

4 optimal design points (green), 25 % each*

c-Design for ED50:

3 optimal design points (red) with weights 25%, 50%, 25%



*Holland-Letz, T. & Kopp-Schneider, A. (2015)

4b. Pharmacokinetics

Simple elimination function:

$$f(t) = \alpha\, e^{\beta t}$$

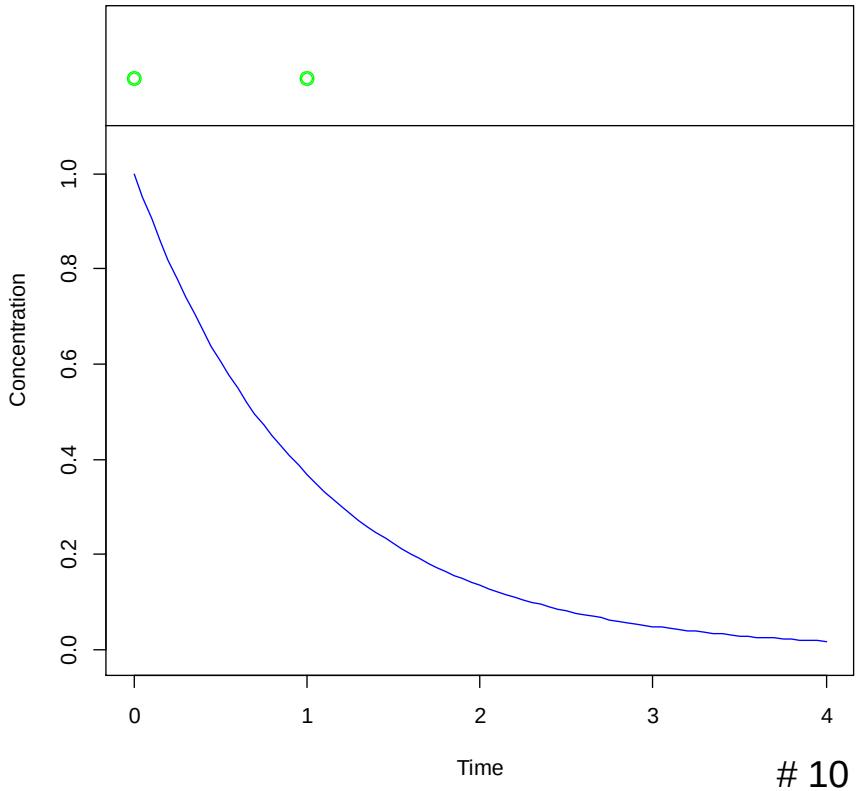
D-Design:

2 optimal design points (green),

50 % weight at $t = 0$ and at $t = \frac{1}{\beta}$

- Any other function possible
- This talk focuses on dose response

α =1, β=1:

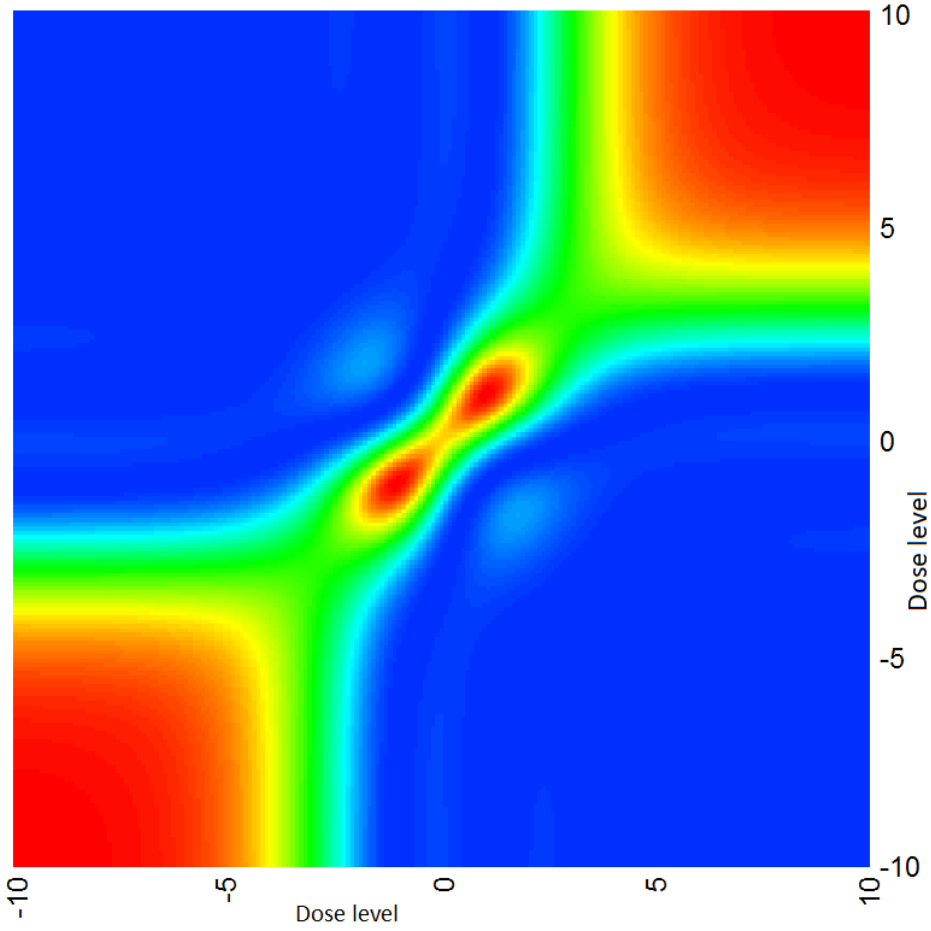


5. The Design Heatmap for D optimality*

- Shows scalar products between information vectors of individual Dose levels, normalized by variance matrix of the optimal design

- Red: Identical information

- Other colors: less similarity



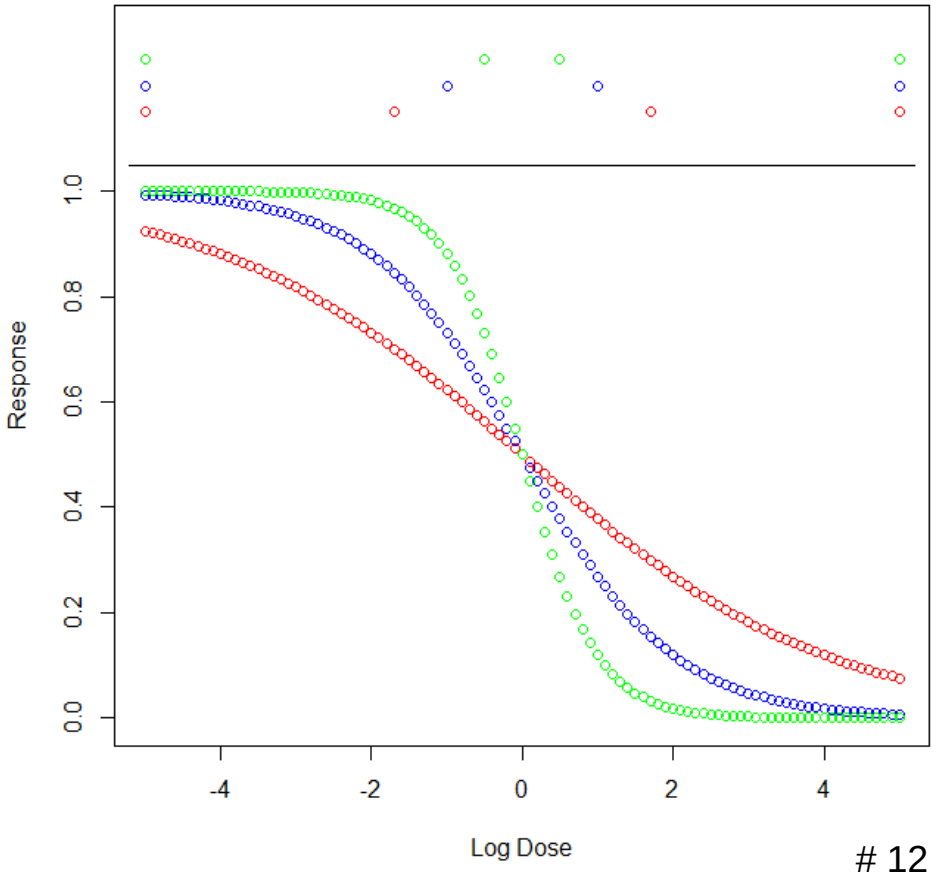
*Holland-Letz, T. & Kopp-Schneider, A. (2020a)

6. Dependence on parameters

Different parameters:

Log-logistic function with
3 different slope parameters
b (red, blue, green).

Result: Still 4 optimal dose levels (top part), 25 % of measurements each.



7. Statistical Optimal Design: Limitations

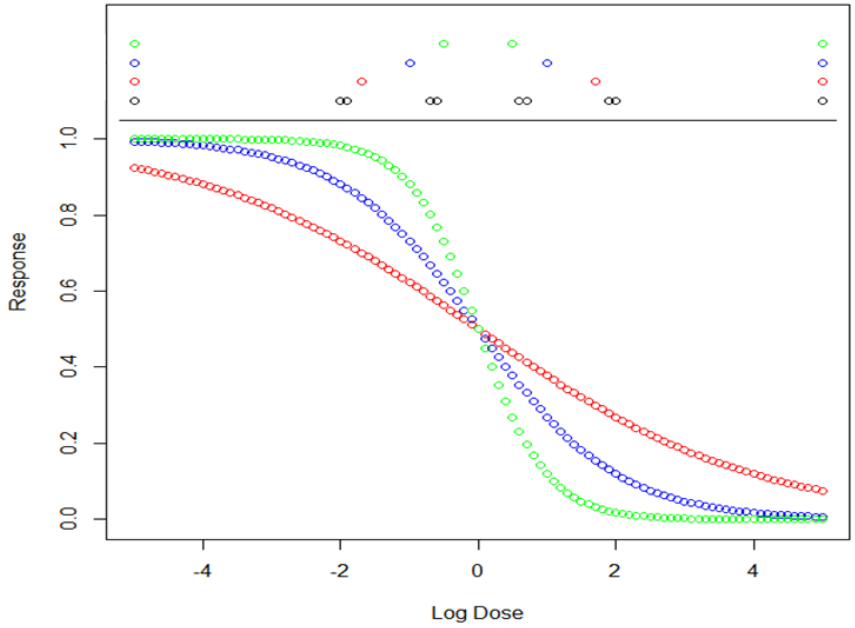
- Problem: Design depends on true parameters
- Wrong parameter assumptions-> poor Designs

True b	True e	Efficiency Log-logistic
1	1	100% (Reference)
0.9	1	99.5%
1	0.9	99.8%
0.9	0.9	99.3%
1.1	1.1	99.6%
0.5	1	91.0%
1	0.5	91.8%
0.5	0.5	89.5%
1	2	91.8%
2	1	75.5%
2	2	61.1%

7. Statistical Optimal Design: Limitations

- One Solution: Quasi-Bayes approach
- Assume probability distribution for parameters
- Optimize expected value of information function over distribution

Example: Parameter b either 0.5, 1 or 2, probability 33.3% each



Quasi-Bayes optimal design shown in black

8. Practical implementation

- Practical scientists usually prefer simple designs
- Most common: Designs with 8 doses equally spaced on the log axis, same number of observations per dose level, plus 20% control
- Best factor: 3^(1/b) for 8 doses, 3.5^(1/b) for only 6 doses
- These designs are still generally 15-30% inferior, but more robust in regard to assumptions about parameter *e*
- Solution: Use a simple design still reasonably efficient

9. Combination experiments

Situation:

Substances are mixed to increase effectiveness

Idea:

Measure, how much more substance is needed, compared to an additive Effect.

Definition of interactions:

Additive effect is defined by one of several theories about interaction.

Loewe additivity:

Substances can replace each other at fixed ratios depending on effect level.

Interaction Index Tau:

Factor describing the change in necessary dose

Tau=1:	No interaction (additivity)
Tau>1 :	More substance needed (anatagonism)
Tau<1:	Less substance needed (synergy)

9. Combination experiments

Usual setup:

- Substances are mixed in different ratios, e.g. 1:1, 2:1, 1:2 .
- Every mixture is then applied in several increasing doses.
- Setup is called a ray design.
- Single substances are included as additional rays.
- Alternative: Combine substances in all combinations on a grid (matrix design)
- In matrix design, no dose response curves can be fitted

9. Optimal design for Combinations

- Expected parameters for combination rays can be (approximately) predicted under Loewe interaction model and additivity (Holland-Letz, 2020b):

$$e_{AB} = \mathrm{v}e_A + (1 - v)e_B$$

$$b_{AB} \approx \frac{ln\left(\frac{p}{100-p}\right)}{ln\left(v\left(\frac{100-p}{p}\right)^{\frac{1}{b_A}} + (1-v)\left(\frac{100-p}{p}\right)^{\frac{1}{b_B}}\right)}$$

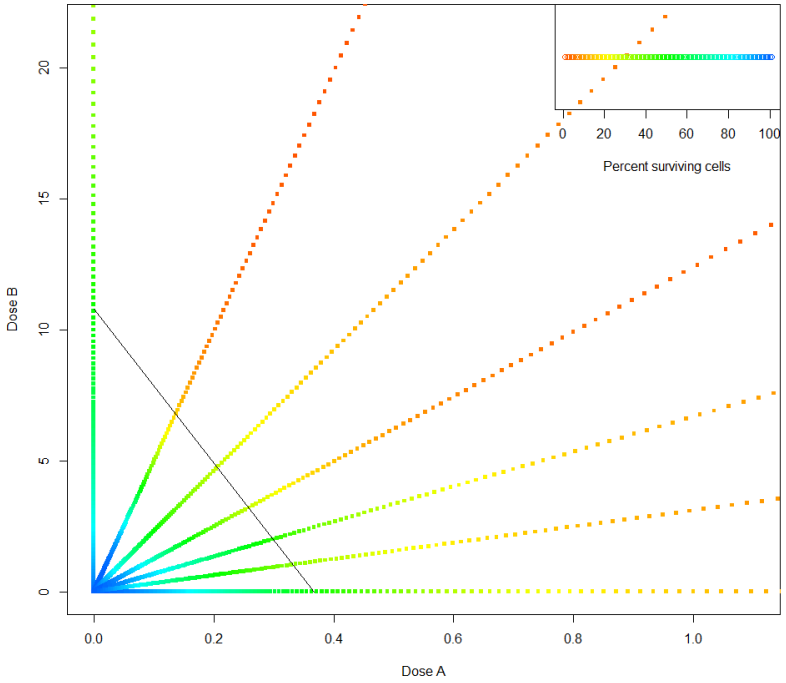
- Every mixture ray is thus just a new standard design problem

9. Optimal design for Combinations

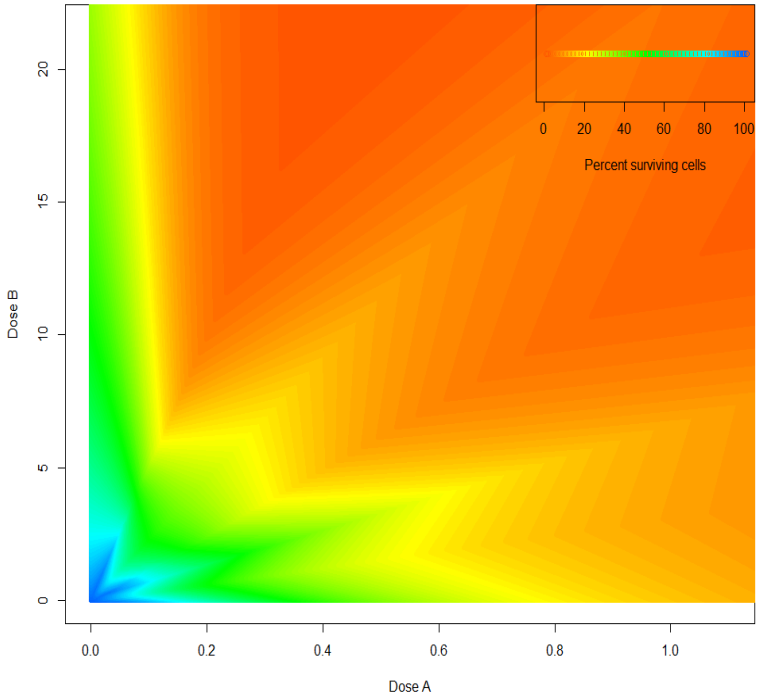
- Interaction index is function of parameters from three rays (two single substances, one mixture)
- D- or c-optimal designs again possible
- c-Designs usually not worth the extra effort (Holland-Letz, T & Kopp-Schneider, A, 2017a)
- Alternative: Fit and estimate parameters for functional relationship between mixture proportion and interaction index / parameters

9. Optimal design for Combinations

Results from a Ray design experiment:



Linear Interpolation



10. An R Shiny Application*

biostatistics.dkfz.de/DoseResponseDesigns/

Optimal Experimental Design for single substance and interaction trials

For details see:
Holland-Letz, T and Kopp-Schneider, A (2020): *An R-Shiny application to calculate optimal designs for single substance and interaction trials in dose response experiments* (under review)

Two different dose response functions can be considered:

$$Log-logistic: y = c + \frac{d-c}{1+\exp^{b(ln(x)-ln(e))}}$$

$$Weibull: y = c + (d-c)\exp^{(-\exp(-b(ln(x)-ln(e))))}$$

Basic settings for design algorithm

Lowest log dose level: -10

Highest log dose level: 10

Number of available dose levels (min 10): 101

Reduction parameter: 0,99

Number of iterations for algorithm (min 50): 500

1. Compute Optimal Designs | 2. Check efficiency of specific designs | 3. Quasi-Bayesian Designs | 4. Compute Optimal Designs for Interactions

This part computes D-optimal designs for a single treatment on the specified design space. One of two available dose response functions can be chosen, and an a priori assumption regarding the assumed slope and ED50 parameters can be made.
Lowering the value for the reduction parameter will try to find a design with fewer support points, but might reduce the efficiency.

Function Parameters

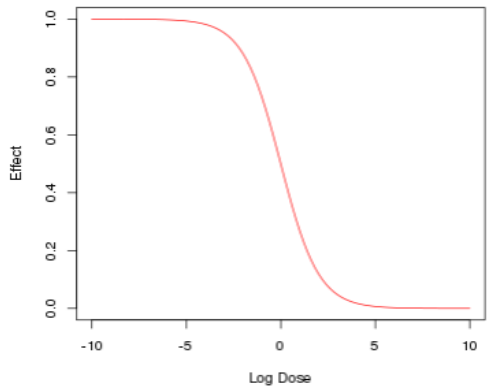
Function:
- (•) Log-logistic
- ( ) Weibull

Slope (Parameter b): 1

ED50 (Parameter e): 1

Compute

Plot of function



*Holland-Letz, T. & Kopp-Schneider, A. (2021)

10. An R Shiny Application

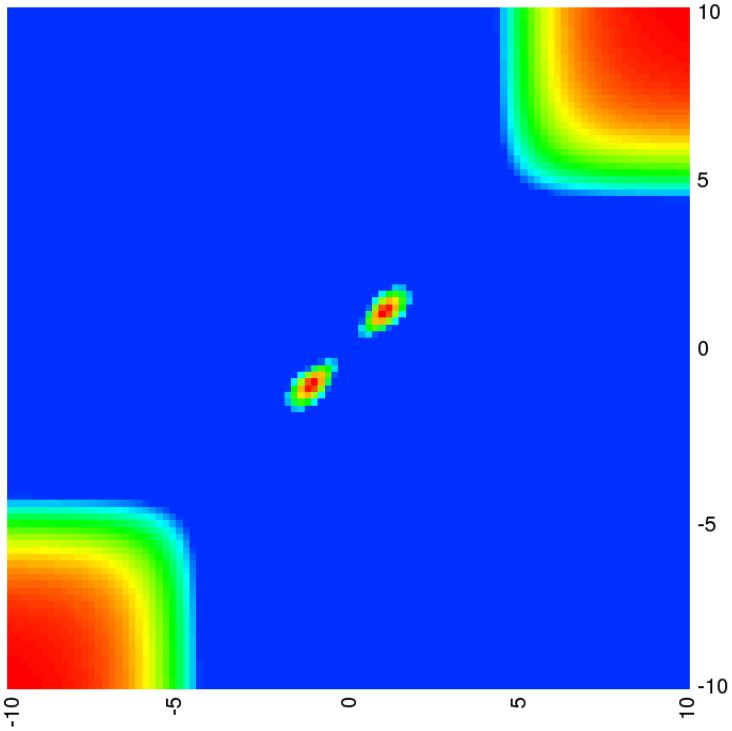
Result

Proposed designs, values of parameters b and e, and resulting D-Efficiency of proposed designs:

	Design	Design	Design	Design	Design	Design	e	b	D-Eff
LogDose	-10.00	-1.20	-1.00	1.00	1.20	10.00	1	1	1.00
Weight	0.25	0.03	0.22	0.22	0.03	0.25	NA	NA	NA

Design Heatmap

Points marked red on the diagonal are potential design points. Pairs of different design points marked red when crossreferenced are interchangeable with negligible loss of efficiency.



11. Extension to substance mixtures

1. Compute Optimal Designs | 2. Check efficiency of specific designs | 3. Quasi-Bayesian Designs | 4. Compute Optimal Designs for Interactions

This part computes D-optimal designs for two singular treatments and up to five combination rays on the specified design space. One of two available dose response functions can be chosen, and an a-priori assumption regarding the assumed slope and ED50 parameters can be made for both singular treatments.
Lowering the value for the reduction parameter will try to find a design with fewer support points, but might reduce the efficiency.

Function Parameters

Function:

- (•) Log-logistic
- ( ) Weibull

Slope Substance A (Parameter b): 1

ED50 Substance A (Parameter e): 1

Slope Substance B (Parameter b): 1,2

ED50 Substance B (Parameter e): 2

Mixtures

 # mixture proportions (max 5): 1

Which Heatmap to plot? (1,2:Single, 3+:Combinations) 1

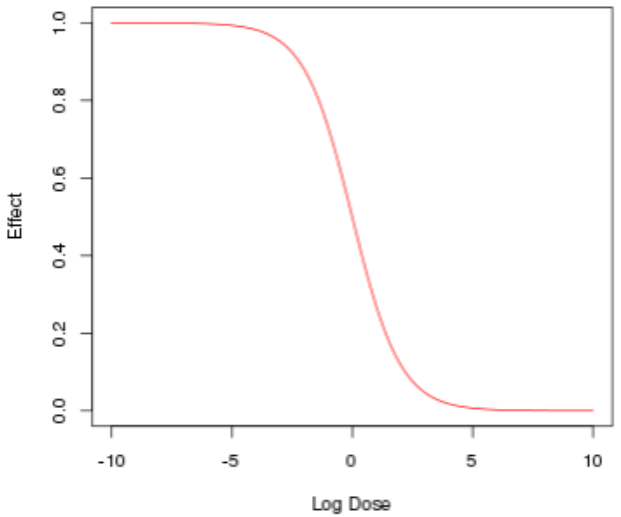
Mixture Proportion 1: 0,5

Combination Index 1: 1

Compute

Click the Compute button to calculate or update the results below.

Plot of function (Parameters A)



12. Summary

- Designs for common dose response situations can be determined algorithmically
- Existing designs can be evaluated, and compromise designs found
- Substance combinations in ray designs can be planned as well
- An R-Shiny app for most of this is available under http://biostatistics.dkfz.de/DoseResponseDesigns/
- Main paper for Shiny app: Holland-Letz, T. & Kopp-Schneider, A. (2021)

Literature

Holland-Letz, T. and Kopp-Schneider, A. (2015). *Optimal experimental designs for dose response studies with continuous endpoints.* Archives in Toxicology, 89(11):2059-68

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Objectives:
Provide a forum to discuss and advance statistical topics related to Research, Discovery, Regulatory and Investigative Toxicology/Safety
(see www.psiweb.org/sigs-special-interest-groups/pre-clinical)

Contact:
Eloisa Brook (eloisa.i.brook@gsk.com) or anyone else of the core committee.

PSI Pre-Clinical SIG

Upcoming events

Webinar 21st June: Regression to the mean, dilution and bridging studies illustrated in R., Dr. Bernard Francq, GSK

Workshop 19th/20th September: 1.5 days including a short course on the application of Bayesian Methods in a Pre-Clinical Environment by Bruno Boulanger.

Webinar 4th October: Therioepistemology: Rethinking how we conduct animal-based experimentation, Dr. Brianna Gaskill, Novartis