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Experimental designs for preclinical dose response experiments

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Life forward

Background

- Verification of a **proof-of-concept** and identification of a **dose response relationship** are key goals in early research when developing pharmaceutical compounds

What are the advantages of *experimental design*?

In general, efficient experimental designs:

- maximize the amount of information
- increase the statistical power and precision

  (or reduce the number of required animals)

Background

Purpose of preclinical studies:

- Analyze safety, efficacy and pharmacokinetics of potential drug candidates
  - **In vitro** studies: Laboratory tests using cell cultures / isolated tissues
  - **In vivo** studies: animal studies
- **Regulations and guidelines** (FDA, EMA, ICH), Good Laboratory Practice
- Crucial for design of clinical trails, regulatory approval and **safe drug development**
- Essential for **understanding dose response relationships** of potential drugs and providing **guidance on human dose estimation** for clinical trails

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Background

What are the challenges in preclinical studies?

- **Sample size calculations** often based on **small data sets** and vague assumptions
- **Practical considerations**: more simple designs are favored
- True underlying dose-response relationship unknown in planning stage
- "**Three Rs Principle**" (Replacement, Reduction, Refinement)

In addition, sample size calculations should be (approximately) valid for various experiments including different compounds.

→ **Robust experimental designs needed**

Setting

Common simple parallel design:

- Response Y is observed for N experimental units, with $\mathrm{N} = \sum_{\mathrm{i}=1}^{\mathrm{k}} \mathrm{n_i}$ of all k dose groups (d_1(negative control), … , d_k)
- $\mathrm{Y}_{ij} = \mathrm{f}(d_i, \theta) + \varepsilon_{ij}\ ;\ \varepsilon_{ij} \sim \mathrm{N}(0, \sigma^2);\ \mathrm{i} = 1, \ldots, \mathrm{k};\ \mathrm{j} = 1, \ldots, n_i$
  - Y_{ij} measurement of individual j within dose group i
  - $\mathrm{f}(., \theta)$ dose-response model with model parameters θ
- **One factorial design**
  - no hierarchies
  - no additional covariates
  - no repeated measurements
- **How should dose levels and corresponding sample sizes be chosen?**

MCP-Mod

- Combines **M**ultiple **C**omparison **P**rocedure and **Mod**eling techniques
  1. Set of **multiple candidate** parametric **models**
  2. Calculation of **optimal contrast tests** for each model in candidate set
  3. **Evaluate significance** of individual models → **Proof-of-concept** for non-flat dose response shape
  4. **Select** most significant **model**
  5. **Model fit** (estimation of model parameters)
  6. **Target dose** estimation
- Considers uncertainty of model selection due to several candidate models
- Uses multiple comparison to choose model most likely

Bayesian MCP-Mod

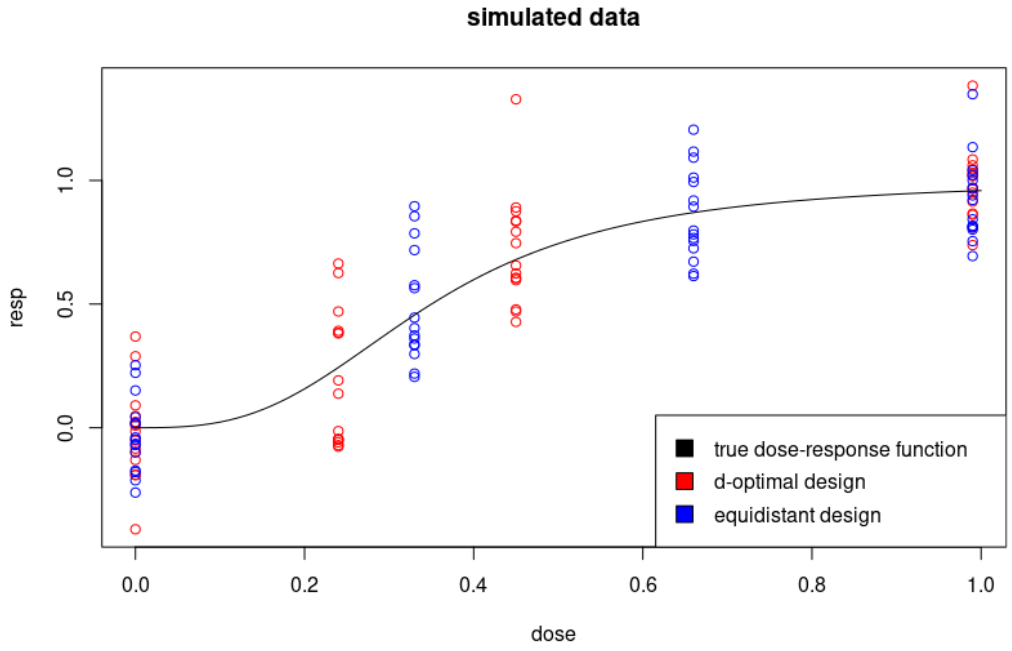
- Often: **Historical data** (for control group) available
- **Bayesian analogue to frequentistic MCPMod** *(Fleischer F, Bossert S, Deng Q, Loley C, Gierse J. Bayesian MCPMod. Pharm Stat. 2022 May;21(3):654-670. doi: 10.1002/pst.2193. Epub 2022 Jan 21. PMID: 35060298.)*
- BMCPMod allows to incorporate historical information into MCPMod approach
  - Inclusion of historical data in systematic fashion
  - Mimics results of classical MCPMod for non-informative priors
- Historical information should be compatible with the new data
- Informative priors for control group and active dose groups possible

D-optimal design

- **Goal**: minimize number of required experimental units to obtain desired precision
- D-optimal designs optimize regarding **estimation of model parameters**
- Calculate matrix F containing the derivatives of the dose-response function f in direction of all parameters
- Variance $\boldsymbol{V}$ for a parameter estimate is given by
- $V \approx \sigma^2 (FF^T)^{-1}$ with σ the standard deviation of the errors
- **Maximize** $\mathrm{Q} = \mathrm{FF}^{\mathrm{T}}$
- D-optimality: maximize determinant of Q
- Optimal design depends on **prior estimates** of dose-response function parameters: **locally optimal** designs
- **Bayes optimal designs**: instead of specifying single parameter guesses, hand over multiple possible parameters with associated probability → Bayes optimal design maximizes average information

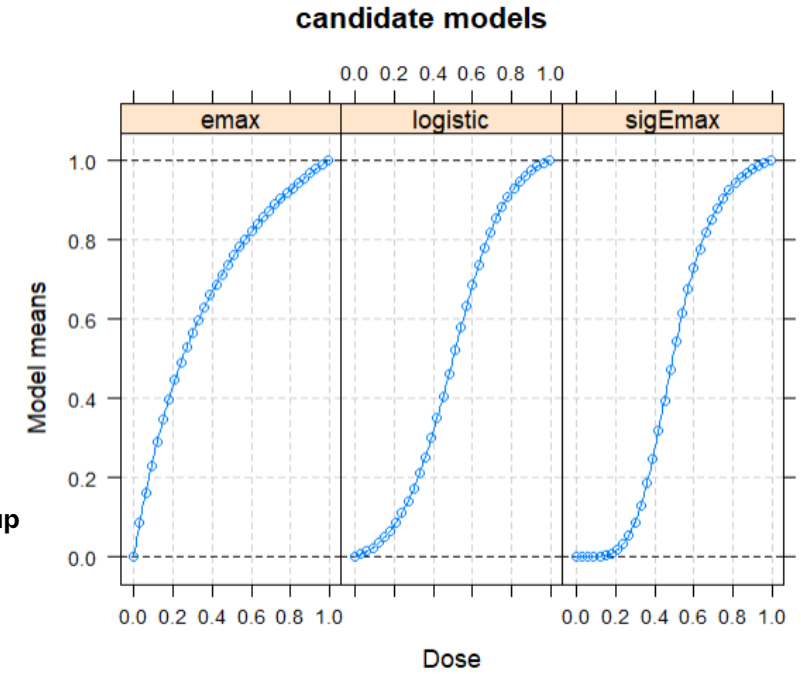
Simulations - Setting

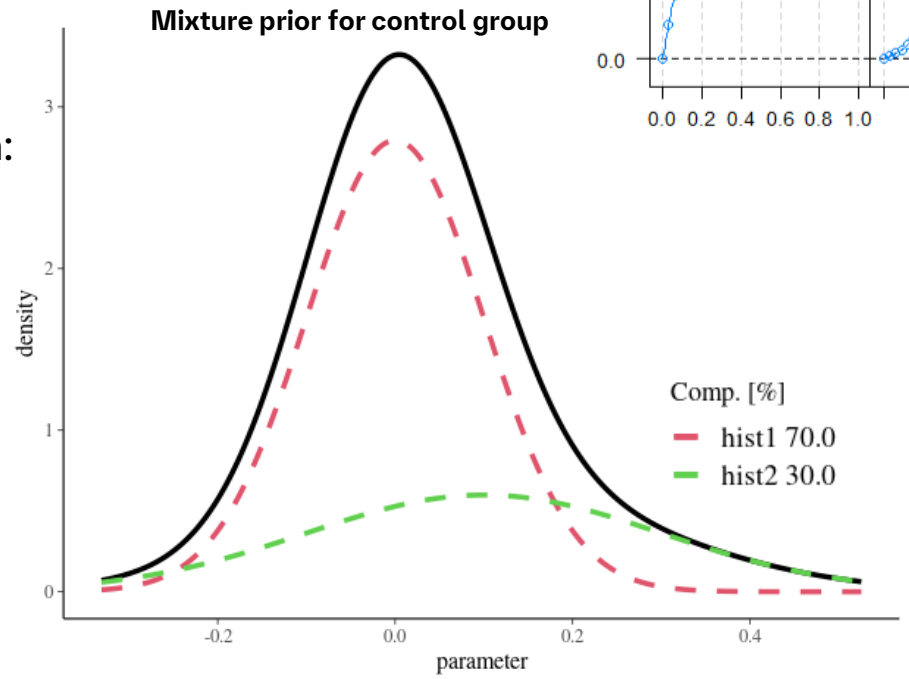
- **Goal:** Compare **precision** of estimated dose response curves of different allocations of dose levels
- Simulate **normally distributed data** and estimate dose response curve with MCP-Mod procedure
  - Include prior information for historical control data for Bayesian MCP-Mod approach
- **Parametric bootstrap:**
  - **M = 10000** bootstrap replicas
- True underlying dose-response curve
  - **Sigmoid Emax Model**: $f(d,\theta) = 0 + (1 * d^3)/(0.35^3 + d^3)$
    - $E0 = 0, Emax = 1, ED50 = 0.35, h = 3$
- Homoscedastic standard deviation in all dose groups = 0.2
- Total sample size N = 60



Simulations – Prior knowledge

- **Three candidate models:**
  - Emax ($ED50 = 0.5$)
  - SigEmax ($ED50 = 0.5, h = 4.7$)
  - Logistic ($ED50 = 0.5, delta = 0.14$)
- Model selection criteria: AIC
- **Prior Information** from historical control data:
  - 2 historical control samples
    - $Mean = 0,\ SD = 0.1$
    - $Mean = 0.1, SD = 0.2$





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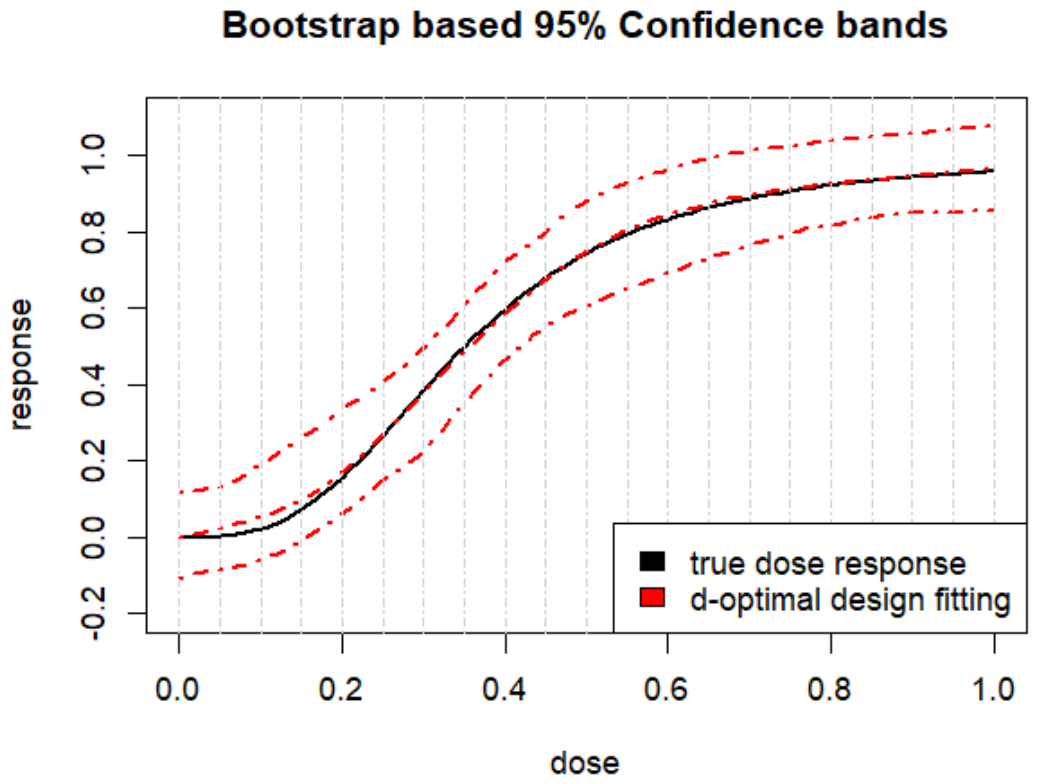
Simulations – Comparison

Comparison criteria for precision of estimates:

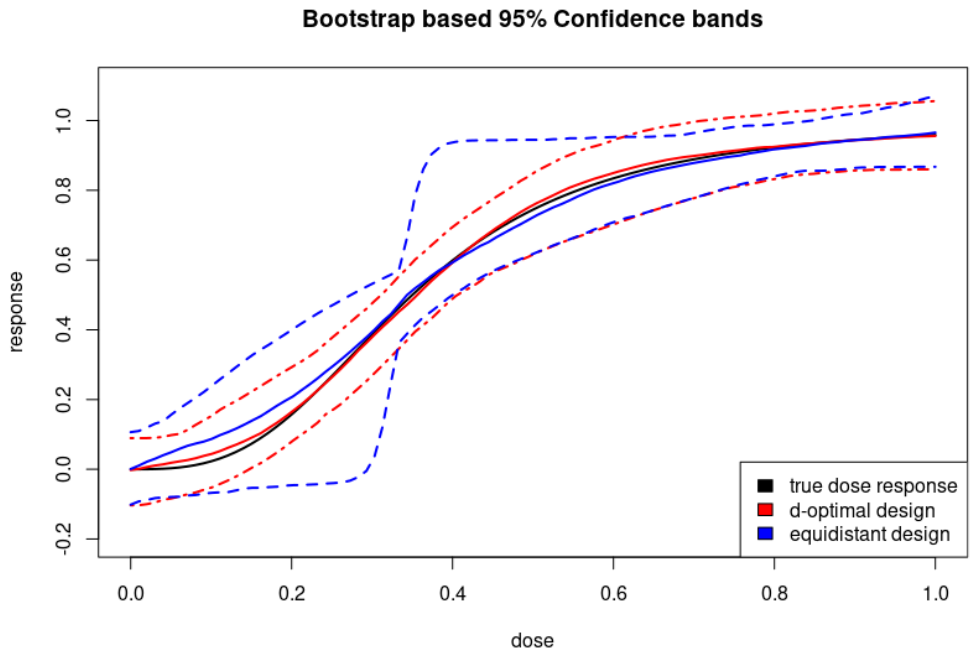
- Bootstrap based pointwise **confidence bands**
  - Divide x-axis into small intervals (e.g., 100 intervals)
  - Calculate point estimators of all fitted curves
  - Calculate 0.025 and 0.975 Quantiles of all point estimates
  - **Area within confidence bands**
- **Median Bias**
- **Selection of model function**



Simulations – optimal scenario

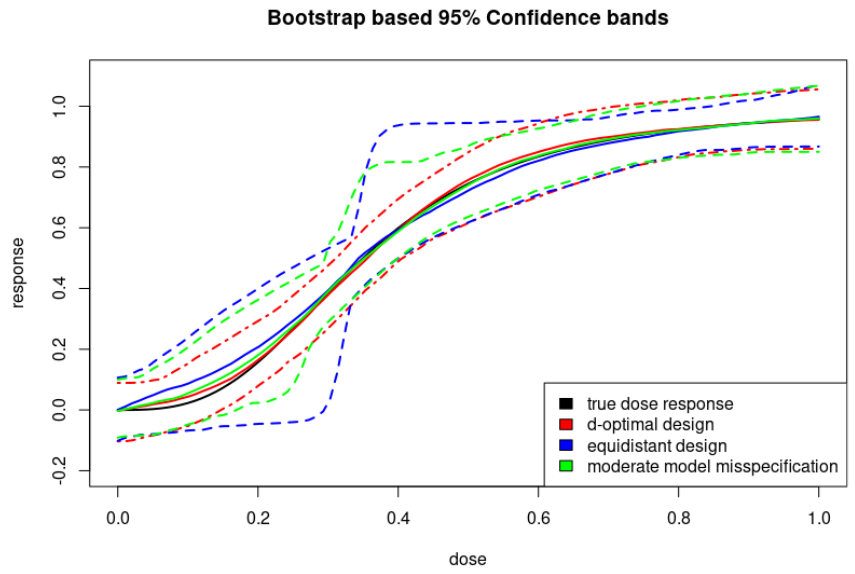
- **D-optimal design vs. 4 balanced equidistant dose levels**
- **More precise** estimators of dose response with
  - D-optimal design
  - Historical control data

Design	Area within 95% Confidence bands	Median Bias
D-optimal design	0.212	0.00013
Equidistant design	0.292	0.00057
BMCPMod d-optimal design	0.182	0.00011
BMCPMod equidistant design	0.253	0.00048



Simulations – moderate parameter misspecification

- Efficiency of d-optimal designs with moderate parameter misspecification
- **Parameter misspecification** for calculation of **d-optimal design**:
    - SigEmax ($ED50 = 0.45, h = 3$) instead of SigEmax ($ED50 = 0.35, h = 3$)
- Loss in precision compared to the optimal design setting, but still much better than in standard setting
    - **Robustness** of d-optimal design



Design	Area within 95% Confidence bands	Median Bias
D-optimal design	0.212	0.00013
Equidistant design	0.292	0.00057
Missp. ED50 (0.45 instead of 0.35)	0.228	0.00017
BMCPMod Missp. ED50	0.213	0.00013

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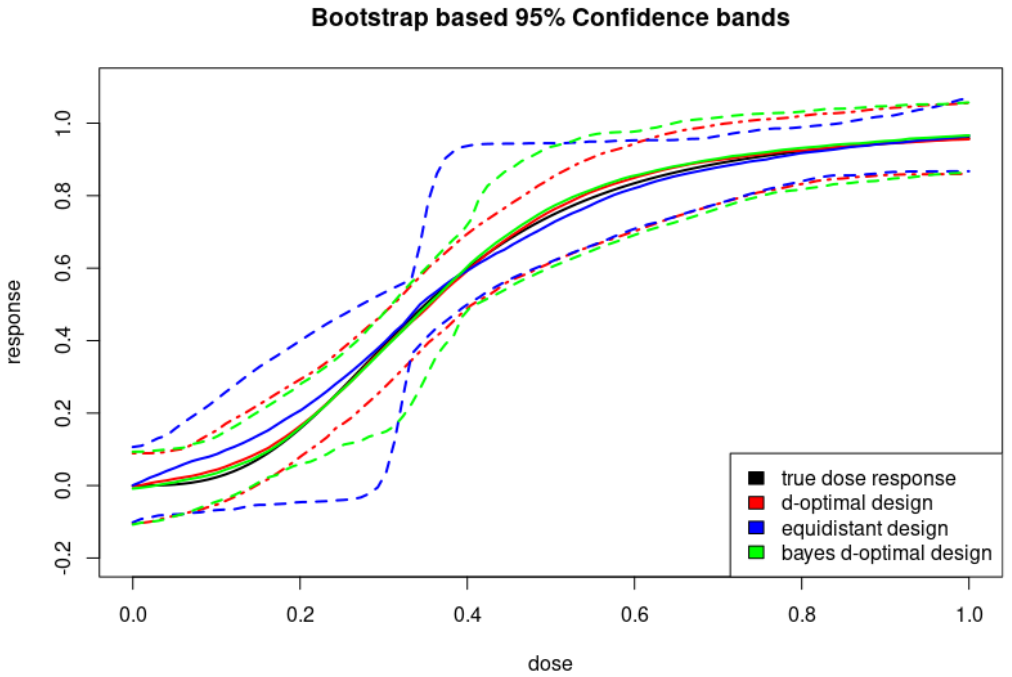
Simulations – selection of final model in %

- Model selection of the MCP-Mod algorithm is crucial for the precision of the estimation

Design	Emax	Logistic	SigEmax
D-optimal design	5.9	44.8	49.3
BMCPMod d-optimal design	5.4	38.3	56.3
Equidistant design	32.2	39.6	28.2
BMCPMod equidistant design	32.6	29.2	38.2
Misspecified ED50 (0.45 instead of 0.35)	13.0	44.6	42.4
BMCPMod misspecified ED50	12.2	35.6	52.2

Simulations – Bayes optimal design

- Larger **parameter uncertainty**
- Idea: give probability distribution of parameters
- **Bayes optimal setting** for calculation of **d-optimal design**:
  - $ED50 = 0.35 \ or \ 0.4 \ or \ 0.5$ each with prob. $1/3$
- In general, **more dose levels** needed
- Precise estimates of dose response function
- **Historical control** data **improves precision**



Design	Area within 95% Confidence bands	Median Bias
D-optimal design	0.212	0.00013
Equidistant design	0.292	0.00057
Uncertain ED50	0.213	0.00015
BMCPMod uncertain ED50	0.200	0.00013

Conclusion

Bayesian MCP-Mod

- Inclusion of historical control data leads to higher precision for informative priors
- Improve robustness and validity

D-optimal designs

- Prior knowledge of model and model parameters needed (although strategy is quite robust to moderate misspecifications)
- More precise estimators of dose response (or reduced sample size)
- Bayes optimal designs: useful for larger parameter uncertainty

In Case of no/very limited initial knowledge

- Larger number of different dose groups advisable

Questions, suggestions, criticism, etc. are always welcome.

Literature

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