Optimal Designs for Drug Combination Studies

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mODa14

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RTG 2624

Biostatistical Methods for High-Dimensional Data in Toxicology

Expertise in statistical modelling and analysis


technische universität dortmund

Department of Statistics:
German center of biostatistics
method development



hhu Heinrich Heine Universität Düsseldorf

Statistical genetics
method development


UNIVERSITÄT ZU KÖLN

Biometrics
method development

Expertise in toxicology (pharmacological toxicology and environmental medicine)

IADO LEIBNIZ-INSTITUT FÜR ARBEITSFORSCHUNG AN DER TU DORTMUND

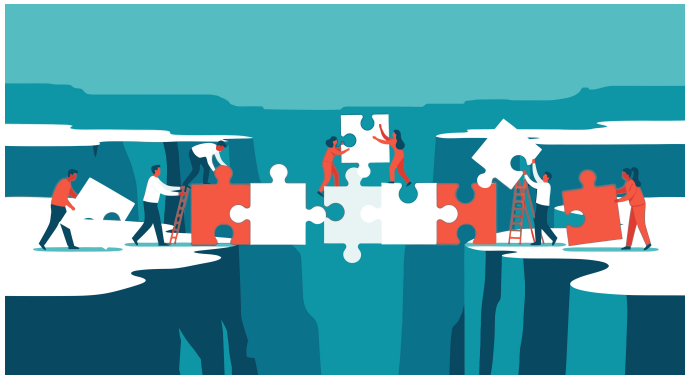
Liver toxicology and pathophysiology, pioneer in systems biology methods for understanding responsible **mechanisms**


IUF LEIBNIZ-INSTITUT FÜR UMWELTMEDIZINISCHE FORSCHUNG


Molecular preventive medical research about environment-induced health disorders, **mechanisms** that are causally involved

Biostatistical Methods for High-Dimensional Data in Toxicology

Aim: Bridge the gap between theory and practice



Project: Optimal Design theory of Experiments in Toxicology

TASKS:

1. Design and Analysis of One-Dimensional Cytotoxity Experiments ✓
2. Implementation of Shiny App for Biologists ✓
3. Providing a Guideline for Designing Cytotoxity Experiments ✓
4. Coping with heteroscedastic errors
5. Detecting Structural Variations between different Experiments
6. Design and Modeling of Toxicity in Mixture Experiments

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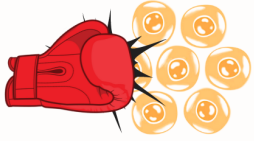
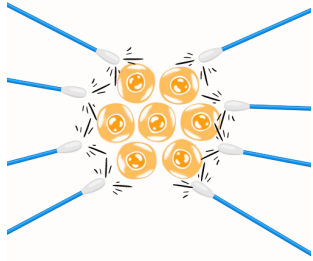
Toxicity in Complex Mixtures: Interaction Effects

- Investigate the toxicity of mixtures to analyze positive or negative interaction effects as the number of substances increases.
- Explore whether mixtures exhibit increasing, decreasing, or constant toxicity as the number of substances increases, using slightly toxic concentrations for each component.



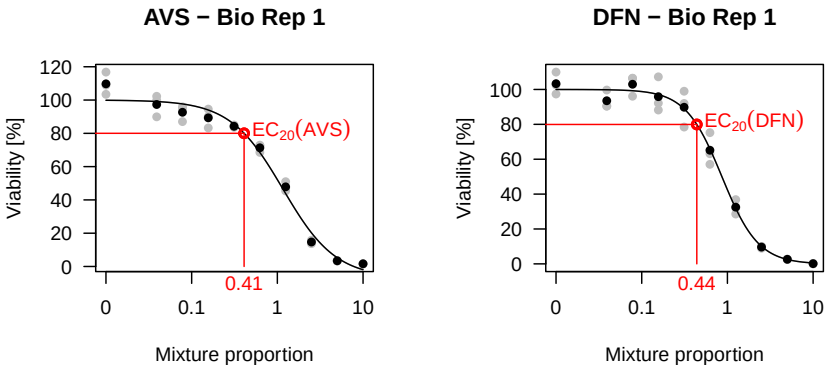
vs.



$1 * EC_{20}$

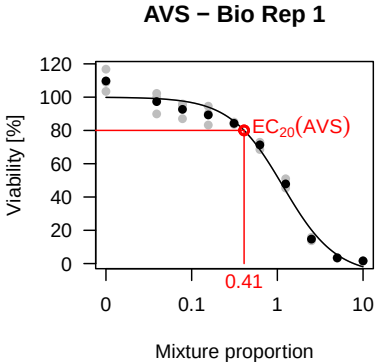
$\sum_{i=1}^{8} \frac{1}{8} * EC_{20,i}$

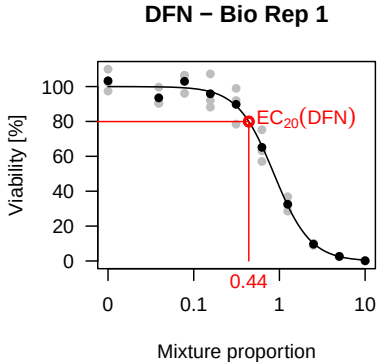
Toxicity in Complex Mixtures: First Approach



- Fit dose-response data to a 4pLL-model $\eta(\cdot, \theta)$, respectively.
- Calculate estimate for EC_p, i.e. $EC_p = \min\left\{x : \frac{\eta(x,\hat{\theta})}{\eta(0,\hat{\theta})} = \frac{100-p}{100}\right\}$

Toxicity in Complex Mixtures: First Approach

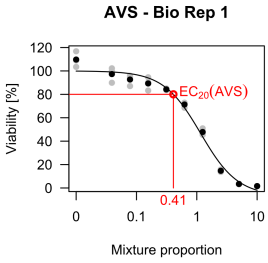


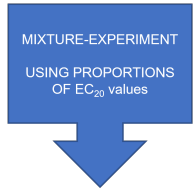


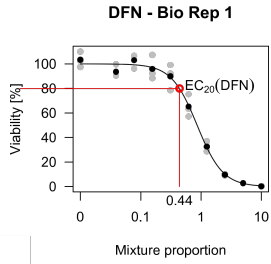
- Use $\mathrm{EC}_{20}(\mathrm{AVS}) = 0.41$ and $\mathrm{EC}_{20}(\mathrm{DFN}) = 0.44$.
- Consider dose combination for $p \in [0, 1]$

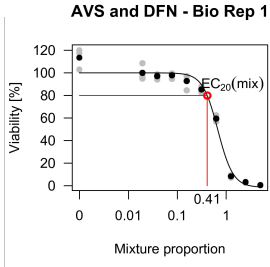
$$d_{\mathrm{mix}} = p \begin{pmatrix} \mathrm{EC}_{20}(\mathrm{AVS}) \\ \mathrm{EC}_{20}(\mathrm{DFN}) \end{pmatrix} = p \begin{pmatrix} 0.41 \\ 0.44 \end{pmatrix}.$$

Toxicity in Complex Mixtures: First Approach









Toxicity in Complex Mixtures: First Approach

- Proportions-Response data is fitted to non-linear regression model:

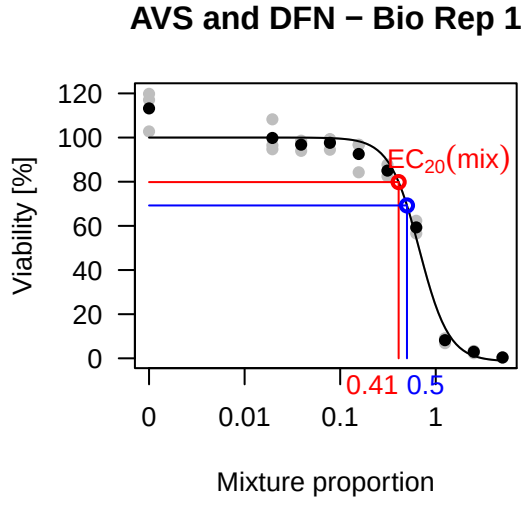
$$\begin{aligned} \hat{\eta}: \quad [0, 1.5] &\to \mathbb{R} \\ p &\mapsto \hat{\eta}(p) \end{aligned}$$

- Calculate the proportion at which the response of 80% is achieved:

$$\mathrm{EC}_{20}(\mathrm{mix}) = 0.41 < 0.5$$

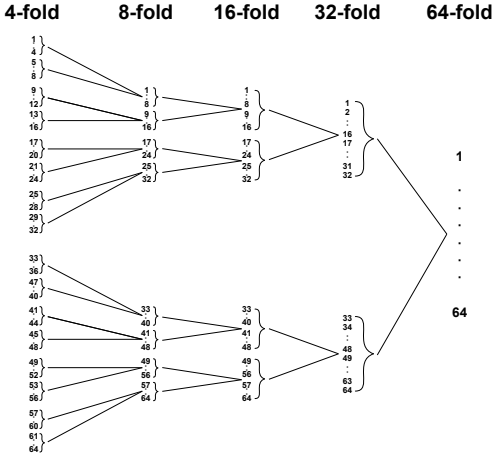
- Check the predicted response at $p = 0.5$:

$$\hat{\eta}(0.5) = 69.25\% < 80\%$$



Toxicity in Complex Mixtures: Experiments in Detail

- Conduct 31 experiments using mixtures containing 2 to 64 substances and the preliminary experiments of the individual substances.

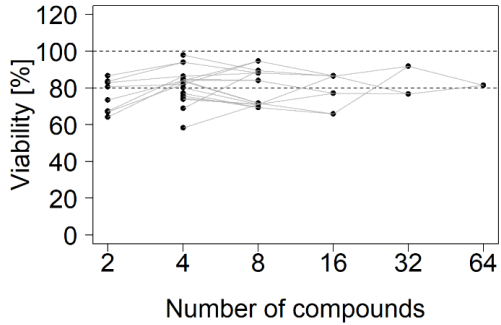


Toxicity in Complex Mixtures: Experimental Results

- Conduct 31 experiments using mixtures containing 2 to 64 substances and the preliminary experiments of the individual substances.

- Each point shows the response of a dose combination.
- For example, let the mixture consist of substances $S_1, \ldots, S_4$:

$$\frac{1}{4}\begin{pmatrix} EC_{20}(S_1) \\ \vdots \\ EC_{20}(S_4) \end{pmatrix} \quad \rightarrow \quad \hat{\eta}_{1,\ldots,4}(\tfrac{1}{4}) = 59.6\%$$



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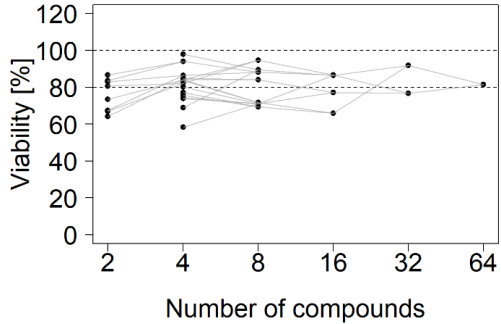
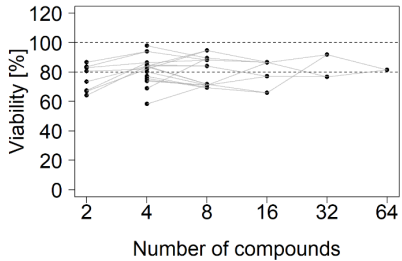


$\Rightarrow$ There do not seem to be any interaction effects...?

Toxicity in Complex Mixtures: Challenges

- The interaction between the substances might be more complex.
  - ⇒ We analyse the case of two substances.
  - ⇒ We not only consider specific proportions of the two substances, but all combinations.
  - ⇒ We use different modeling approaches to catch different interaction types.
- ...

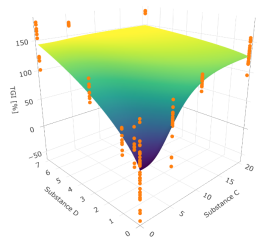


Modeling Dose Combinations

Approach: Analyse the effect of combining two substances C and D by non-linear surface, i.e.:

$$Y_{ij} = \eta((c_i, d_i), \theta) + \varepsilon_{ij}, \qquad i = 1, \ldots, k, j = 1, \ldots, n_i$$

- Dose combinations $(c_i, d_i) \in \mathcal{Z} = [0, c_{\max}] \times [0, d_{\max}]$
- $\eta(\cdot, \theta)$ non-linear surface
- $\theta \in \mathbb{R}^p$ unknown parameter
- TODAY: $\varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2)$ i.i.d.



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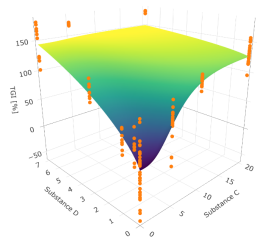


TARGETS:

1. Precise estimation of θ.
2. Precise inference about dose combinations resulting in specific responses, e.g. in 80%.

Different type of models – one goal

The additive interaction model:

$$\eta((c,d),\theta) = \theta_0 + \eta_C(c,\theta_C) + \eta_D(d,\theta_D) + \gamma\,\eta_C(c,\theta_C)\eta_D(d,\theta_D)$$

- η_C, η_D: single–drug dose–response models
- γ: interaction parameter
  - $\gamma > 0$ synergy
  - $\gamma < 0$ antagonism
  - $\gamma = 0$ no interaction

The Greco model:

$$\eta((c,d),\theta) = \frac{\mathrm{E}_{\max} \cdot \left[\frac{c}{\mathrm{ED}_{\mathbf{50}\,C}} + \frac{d}{\mathrm{ED}_{\mathbf{50}\,D}} + \alpha \cdot \left(\frac{c}{\mathrm{ED}_{\mathbf{50}\,C}} \cdot \frac{d}{\mathrm{ED}_{\mathbf{50}\,D}}\right)\right]^{\gamma}}{\left[\frac{c}{\mathrm{ED}_{\mathbf{50}\,C}} + \frac{d}{\mathrm{ED}_{\mathbf{50}\,D}} + \alpha \cdot \left(\frac{c}{\mathrm{ED}_{\mathbf{50}\,C}} \cdot \frac{d}{\mathrm{ED}_{\mathbf{50}\,D}}\right)\right]^{\gamma} + 1},$$

- $\theta = (\mathrm{E}_{\max}, \mathrm{ED}_{50\,C}, \mathrm{ED}_{50\,D}, \alpha, \gamma)$ parameter
- $\alpha > 0$: interaction parameter
  - $\alpha > 0$ synergy
  - $\alpha = 0$ additive interaction

Effective Dose Sets in Combination Studies

In one–dimensional dose–response models:

$$ED_p = \min\left\{ x : \frac{\eta(x,\theta)}{\eta(x_{\max},\theta)} = \frac{p}{100} \right\}$$

Key difference for dose combinations:

- Multiple dose combinations produce the same effect

Multivariate effective dose set

$$\mathrm{MED}_p(\theta) = \left\{ (c,d) \in \mathcal{Z} \;\middle|\; \frac{\eta((c,d),\theta)}{R_{\max}} = \frac{p}{100} \right\}$$

$$R_{\max} = \max_{(c,d)} \eta((c,d),\theta)$$

- MED_p: set of dose combinations achieving p% of the maximal effect
- Geometrically: **contour lines on the response surface**

Dose combinations resulting in the same response

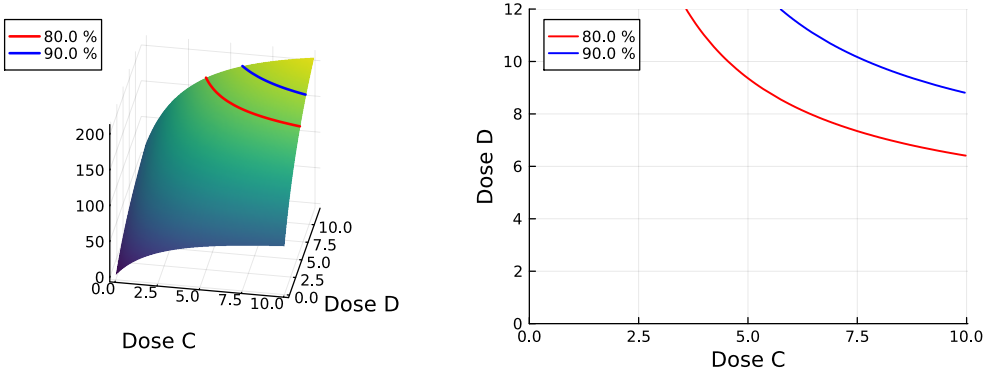


Figure: Response surface and multivariate effective doses.

Optimal Designs for Identifying MED_p

Goal: Precisely identify the sets $\mathrm{MED}_{p_1}, \ldots, \mathrm{MED}_{p_k}$.

Approach:

- Use asymptotic prediction variance at a dose combination $(c, d) \in \mathcal{C}(\theta) = \bigcup_{i=1}^{k} \mathrm{MED}_{p_i}$:

$$\varphi((c,d),\xi,\theta) = \left(\frac{\partial \eta}{\partial \theta}((c,d),\theta)\right)^T M^-(\xi,\theta) \left(\frac{\partial \eta}{\partial \theta}((c,d),\theta)\right)$$

- Choose the design ξ such that prediction variance is small along the relevant MED curves.

Optimality criterion: A design ξ^* is called *locally* MED_q*-optimal* if it minimizes

$$\phi_{\mathrm{MED}_q}(\xi,\theta) = \left(\frac{1}{l_{\mathcal{C}(\theta)}} \int_{\mathcal{C}(\theta)} \varphi^2((c,d),\xi,\theta)\, d\mu(c,d)\right)^{1/q}$$

among all designs ξ on the space $\mathcal{Z}$, where $l(\mathcal{C}(\theta))$ is the length of the considered MED-curves.

Equivalence Theorem for MED_q-optimality

Let ξ^* be an approximate design on $\mathcal{Z}$.
The design ξ^* is locally MED_q-optimal if and only if there exists a generalized inverse $G \in \mathbb{R}^{m \times m}$ of $M(\xi^*, \theta)$ such that the inequality

$$\int_{\mathcal{C}(\theta)} \big(\varphi((c,d),\xi^*,\theta)\big)^{q-1} \alpha^2\big((c_0,d_0),(c,d),\xi^*,\theta\big)\, d\mu(c,d) - \phi^q_{\mathrm{MED}_q}(\xi^*,\theta) \leq 0$$

holds for all $(c_0, d_0) \in \mathcal{Z}$, where

$$\alpha\big((c_0,d_0),(c,d),\xi,\theta\big) = \left(\frac{\partial}{\partial\theta}\eta((c,d),\theta)\right)^T G^T M(\xi,\theta) G \left(\frac{\partial}{\partial\theta}\eta((c_0,d_0),\theta)\right).$$

Moreover, equality is achieved for all (c, d) in the support of the design ξ^*.

Case Study

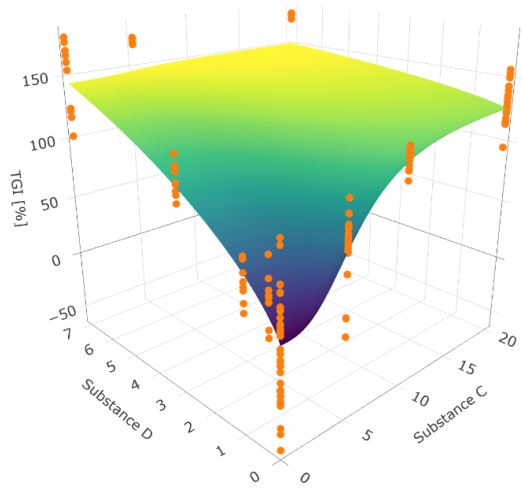


Figure: Drug combination surface model for the TGI in % with sigmoid Emax model for both substances.

Optimal Designs for the Case Study

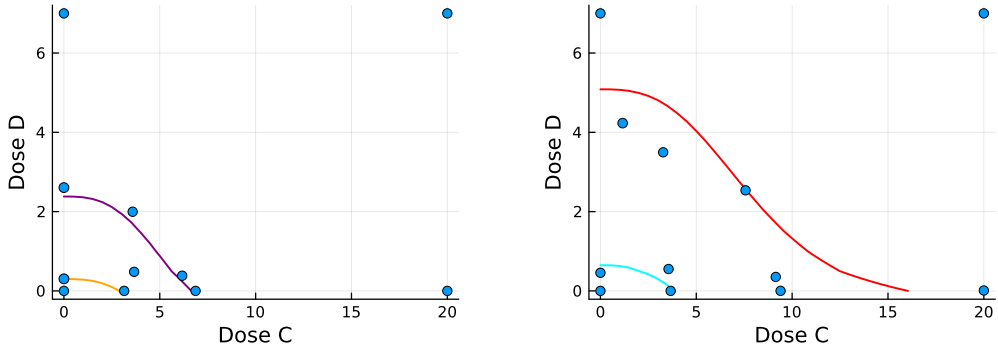


Figure: Optimal designs for MED $(10, 50)$ and for MED $(20, 80)$.

Comparison with respect to efficiency

Design	Levels	
	$(10, 50)$	$(20, 80)$
Ray $4/2$	0.07	0.09
Ray $4/4$	0.06	0.08
Factorial 4×4	0.04	0.06
Original	0.34	0.47
D-optimal	0.6	0.8
MED $(10, 50)$	1.00	0.19
MED $(20, 80)$	0.52	1.00

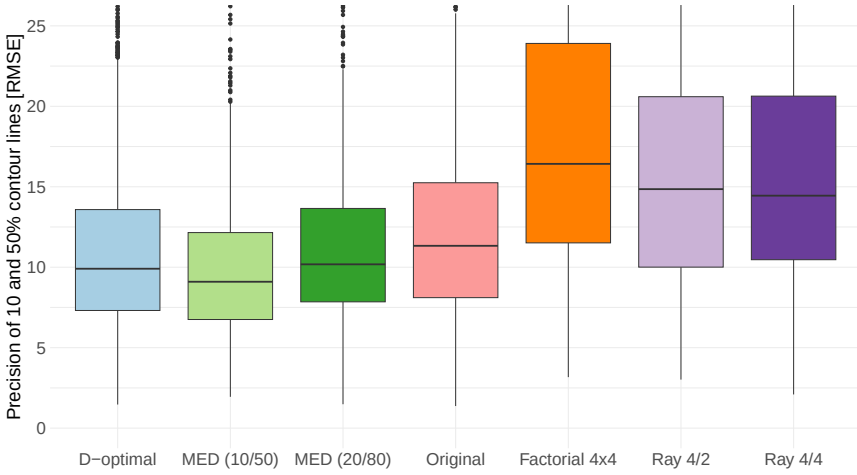
Simulation study - Scenarios

	Scenario 1	Scenario 2
Assumed model	Additive model (sigmoid Emax, sigmoid Emax)	Greco model
Design space	$[0, 20] \times [0, 7]$	$[0, 1] \times [0, 1]$
Parameter	$\theta_0 = 19.05$	$\theta_0 = 0$, $\mathrm{E}_{\mathrm{max}} = 1, \gamma = 2$
	$\theta_C = (111.10, 5.83, 2.86)$	$\mathrm{EC}_{50\,C} = 0.5$
	$\theta_D = (410.82, 20.00, 0.78)$	$\mathrm{EC}_{50\,D} = 0.4$
Interaction	$\gamma = -0.0075$	$\alpha = 0.2$
Contour level(s)	$(10, 50)$	10
Error sd	$\sigma_{\mathrm{CS}} = 24$	$\sigma = 0.45$

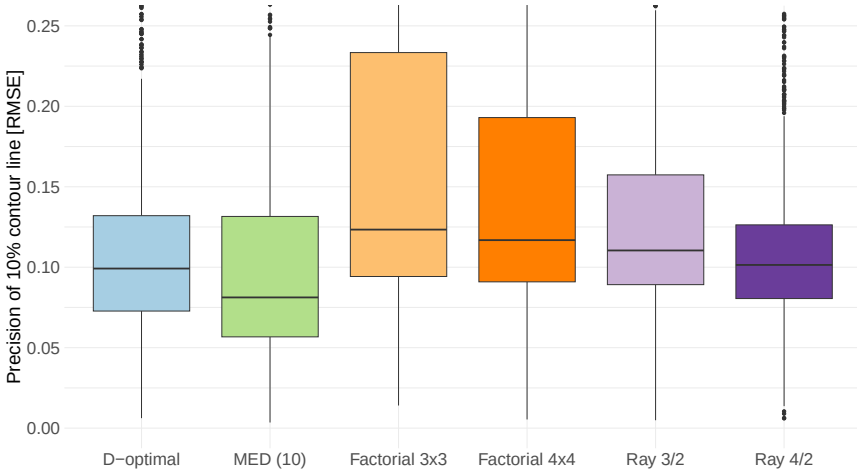
Performance Measure:

$$\mathrm{RMSE} = \frac{1}{k} \sum_{i=1}^{k} \sqrt{\frac{1}{l_i} \sum_{j=1}^{l_i} \left(p_i - \eta((c_j, d_j)_i, \theta_t)\right)^2} \qquad (c_j, d_j)_i \in \mathrm{MED}_{p_i}(\hat{\theta}_s) \quad \text{for} \quad \begin{cases} i = 1, \ldots, k \\ j = 1, \ldots, l_i \end{cases} .$$

Simulation Results: Additive model



Simulation Results: Greco model



Conclusion & Outlook

- Complex Mechanisms should not be simplified too much.
- To understand the high-dimensional situation one should first consider the low-dimensional.
- Two-dimensional setup:
  - There are further numerical and analytical results on MED_q-optimal designs.
  - In any case, the standard factorial designs and the ray designs are outperformed.

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- To understand the high-dimensional situation one should first consider the low-dimensional.
- Two-dimensional setup:
  - There are further numerical and analytical results on MED_q-optimal designs.
  - In any case, the standard factorial designs and the ray designs are outperformed.
- We will extend our findings to the high(er)-dimensional case.
- We currently compare different modeling approaches, particularly for higher number of compounds.
- In the actual mixture experiment there are several reasons for increasing uncertainty. We will develop strategies to cope with these reasons.

Literature

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Additional Material

The standard designs