Optimization of dose finding studies for fixed-dose combinations using nonlinear mixed-effect models

Theodoros Papathanasiou[1,2], Anders Strathe[2], Rune Viig Overgaard[2], Trine Meldgaard Lund[1]

[1]University of Copenhagen, Copenhagen, Denmark,
[2]Novo Nordisk A/S, Sborg, Denmark

Andrew C. Hooker
Associate Professor of Pharmacometrics
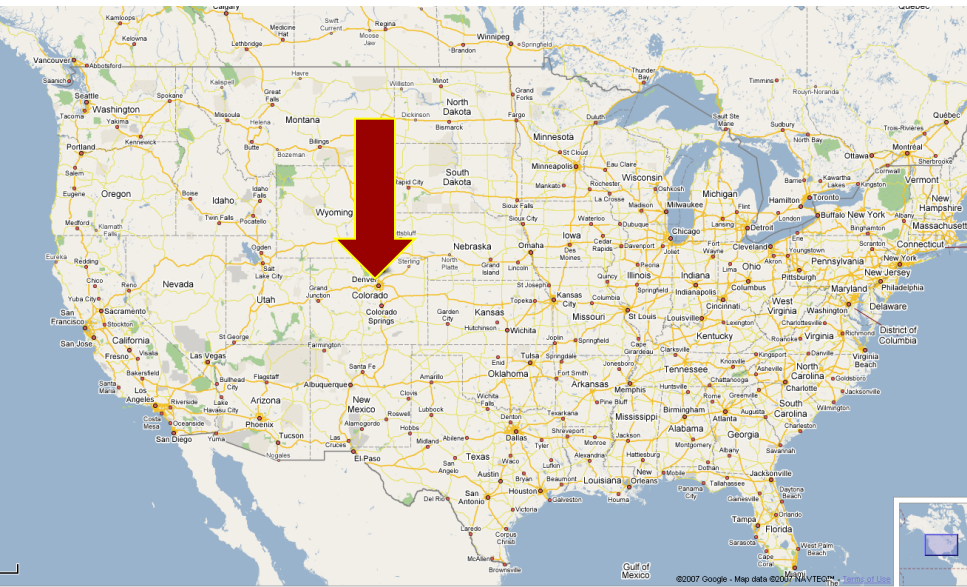Dept. of Pharmaceutical Biosciences
Uppsala University
Uppsala, Sweden

Boulder, Colorado, USA

Pharmacometrics research group in Uppsala, Sweden
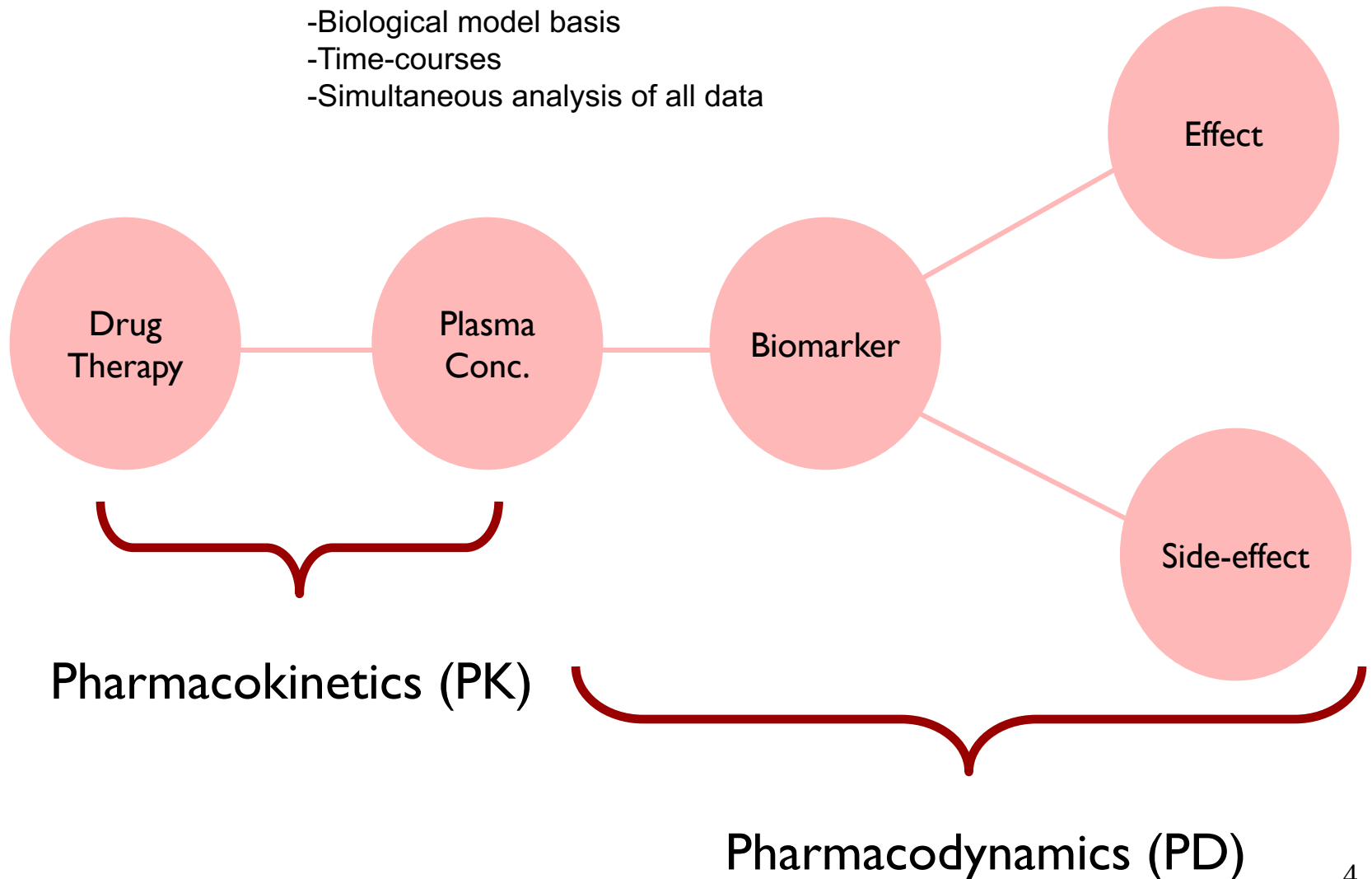
"We develop and use mathematical models to understand drug and disease mechanisms, and to optimise drug development and therapy."

UPPSALA UNIVERSITET

http://www.farmbio.uu.se/forskning/researchgroups/farmakometri/

What is a Pharmacometric model?

-Biological model basis
-Time-courses
-Simultaneous analysis of all data

Pharmacokinetics (PK)

Pharmacodynamics (PD)

The population model

$$y_{ij} = f(\vec{\theta}, \vec{\eta}_i) + h(\vec{\theta}, \vec{\eta}_i, \vec{\varepsilon}_{ij})$$

- y_{ij} The ith individual's jth observation.

- $f()$ A model that describes all observations

- $\vec{\theta}$ A vector of the typical individual parameter values

- $\vec{\eta}_i$ A vector of the ith individual's deviation from the typical parameter values.

- Ω A matrix of the variances and covariances of $\vec{\eta}_i$

- $\vec{\varepsilon}_{ij}$ A vector of the ith individuals, jth residual error.

- Σ A matrix of the variances and covariances of $\vec{\varepsilon}_{ij}$

- (other levels of variability, covariates, …)

Dose finding studies for fixed-dose combinations

- **Targeted drug therapies – optimize delivery to a target** … but may be suboptimal in a physiological system that has evolved to be regulated by a multiplicity of pathways.

- Combinations of drugs may give higher clinical benefit, especially when the combined drugs act via synergistic interactions.

- This complicates the dose selection phase of drug development!

Have we seen these types of situations in other talks this week?

Design of Experiments: New Challenges
Plans d'expériences : nouveaux défis
30 April - 4 May 2018

Conference Program

Monday, April 30

9:15 – 9:30	Welcome & opening session
9:30 – 10:30	Data selection

J. Stufken, Information-based optimal subdata selection
H. Wang, Statistical inference based on optimal subdata

Coffee break

11:00 – 12:00	Optimal design 1: polynomial models

F. Gamboa, Approximate optimal designs for multivariate polynomial regression
H.P. Wynn, Hilbert series and polynomial models for Smolyak-type sparse grid designs

Lunch break

14:30 – 16:00	Algorithmic constructions

U. Grömping, An algorithm for generating good mixed level factorial designs
R. Harman, Computing D-optimal designs of experiments on finite spaces: a survey and comparison of algorithms
S. Leonov, Implementation of algorithms of optimal experimental design on a quantum computer

Coffee break

16:30 – 17:30	Optimal design 2

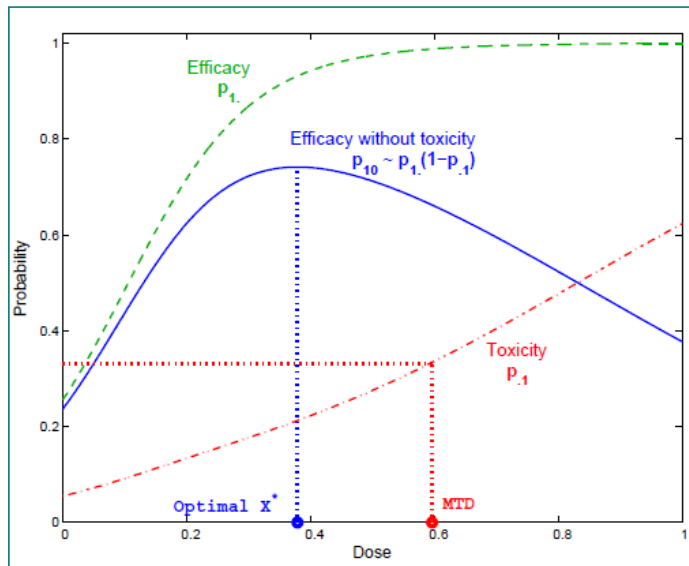**A.C. Atkinson,** Experiments for determining non-isothermal kinetic rates
K. Schorning, Optimal designs for enzyme inhibition kinetic models
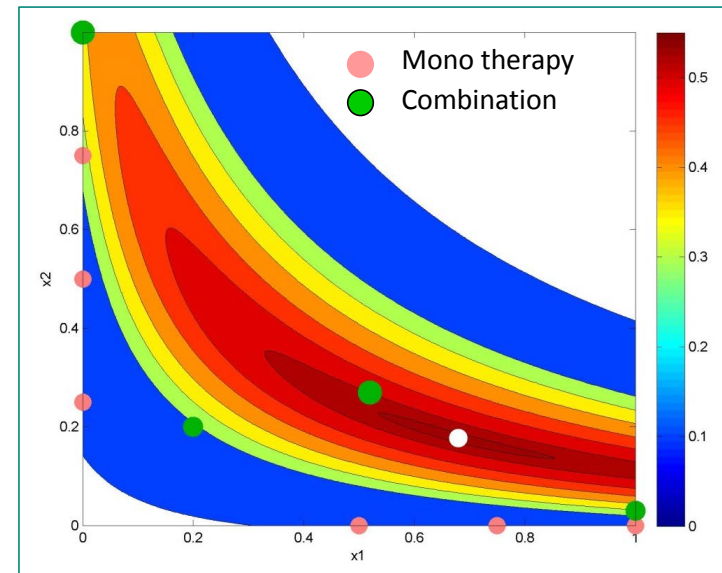
Have we seen these types of situations in other talks this week?

Dose finding: efficacy – toxicity balance

Single drug: maximize probability of efficacy w/out toxicity

Drug combination: borrowing information between studies (composite designs)

Fedorov, Leonov (2013), Chapters 6, 8

Slide provided by S. Leonov

Overview

- Combination model
- Standard designs for these types of systems
- D-optimal Design
- Designs including uncertainty
- Focused designs
  - Ds Optimal Design
  - IV Optimal Design
  - Compound D-IV Optimal Design

$$E_A = \frac{E_{Max,A} \cdot C_{ss,A}{}^{\gamma_A}}{EC_{50,A}{}^{\gamma_A} + C_{ss,A}{}^{\gamma_A}} \qquad E_B = \frac{E_{max,B} \cdot C_{ss,B}{}^{\gamma_B}}{EC_{50,B}{}^{\gamma_B} + C_{ss,B}{}^{\gamma_B}}$$
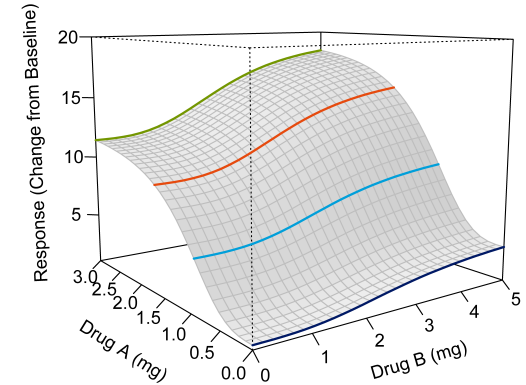
$$C_{ss,X}(Dose) = \frac{Dose_x \cdot F_X}{CL_{X,i} \cdot \tau} \qquad CL_{X,i} = \theta_X\, e^{\eta_{X,i}} \qquad \eta_{X,i} \sim N(0, \omega_X^2)$$

$$E = E_0 + E_A + E_B + \alpha E_A E_B + \varepsilon, \qquad \varepsilon \sim N(0, \sigma^2)$$

$$a = \begin{cases} Possitive\ Interaction, & a > 0 \\ Lack\ of\ Interaction, & a = 0 \\ Negative\ Interaction, & a < 0 \end{cases}$$

- Change from baseline model
- Assumes steady state Concentrations
- Only between subject variability on Css, which is assumed known
- End-of-study, cross-sectional analysis

Right dose combination identification

The dose combination that leads to a wanted pre-specified effect (typical value or percentile in a distribution)

Modelling approach allows us to answer two different questions

– What is the "best dose combination" amongst the doses tested in the in a phase II program

– What is the "right combination" when this is outside the phase II program

• A phase IIb may be needed if this combination dose is chosen to be pursued

Correct dose identification

- Selection of the "right dose" for a given desired effect level, for the doses that were part of the study

- Probability that the studied combination dose will lead to a wanted effect, based on 1000 SSEs with uncertainty in parameter estimates
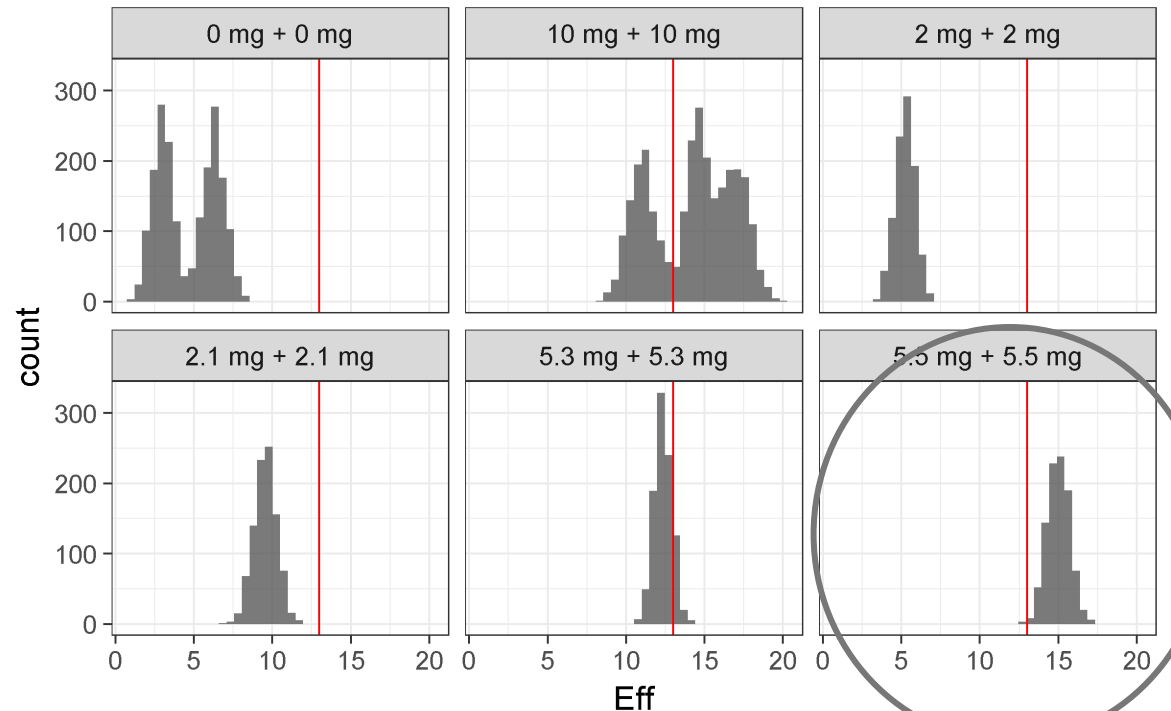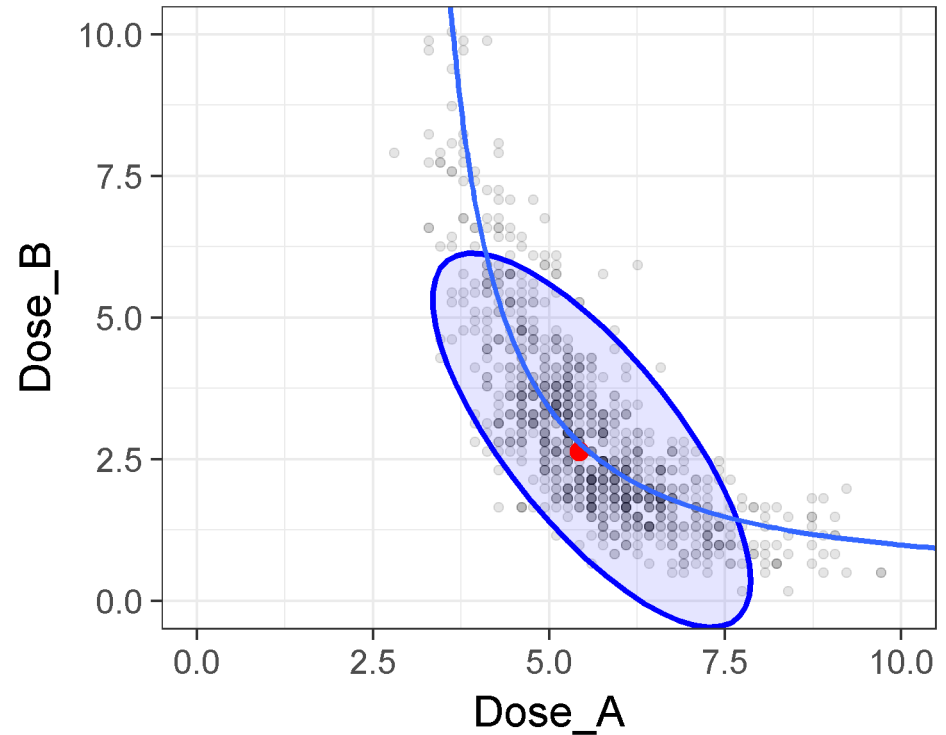

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Correct dose identification

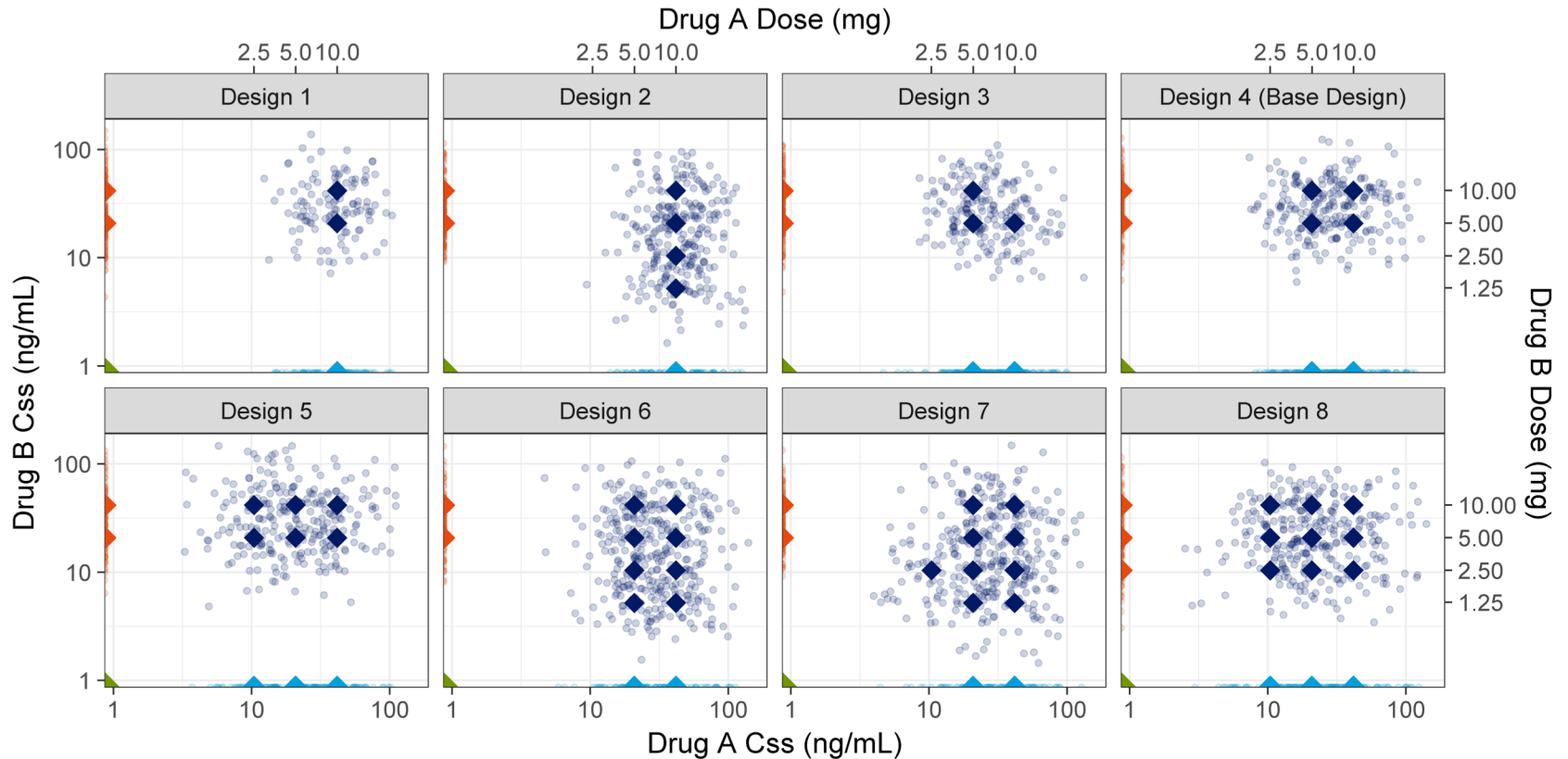Best dose defined as the *smallest* combination of both drugs leading to a wanted effect

Steps:

- Predict DER isobole of interest from estimated parameter vector (with parameter uncertainty)

- Identify the combination of doses that minimizes the distance from the origin

"Standard" designs

Papathanasiou et al.,
"Feasibility of Exposure-Response analyses for clinical dose-ranging studies of drug combinations",
AAPSJ, Accepted, 2018.

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Parameter scenarios

| Parameter (unit)	Parameter Value				Description
	Scenario 1	Scenario 2	Scenario 3	Scenario 4	
E_0 (%)	3	3	3	3	Baseline effect
$E_{max,A}$ (%)	9	9	9	9	Maximum drug effects for Drug A
$EC_{50,A}$ (ng/mL)	20	20	20	20	C_{ss} leading to half maximal effect for Drug A
γ_A	2	1	1	2	Sigmoidicity factor for Drug A
$E_{max,B}$ (%)	4.5	9	4.5	11.25	Maximum drug effect for Drug B
$EC_{50,B}$ (ng/mL)	20	20	20	20	C_{ss} leading to half maximal effect for Drug A
γ_B	1	1	1	1	Sigmoidicity factor for drug B
α	0.15	0	0.15	-0.05	Pharmacodynamic interaction parameter
σ (%)	6	6	6	6	Additive residual error (standard deviation)

Dose for Drug A or Drug B to achieve half maximal: 4.8 mg (25% CV)
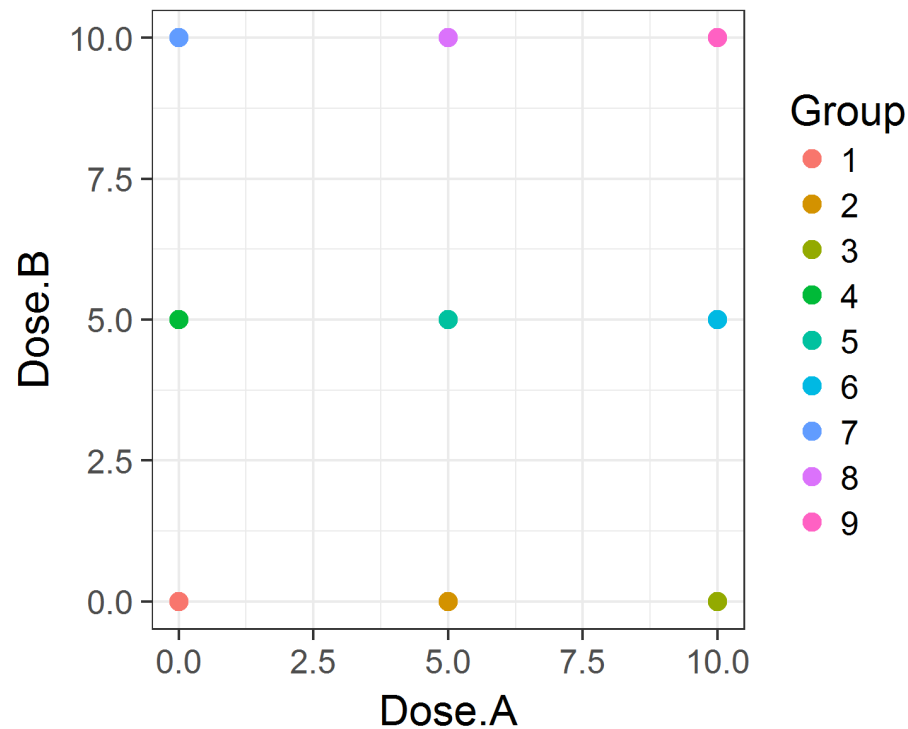
$$C_{ss,X}(4.8) = EC_{50,X}$$

Evaluated Response surfaces

Evaluated E-R surfaces
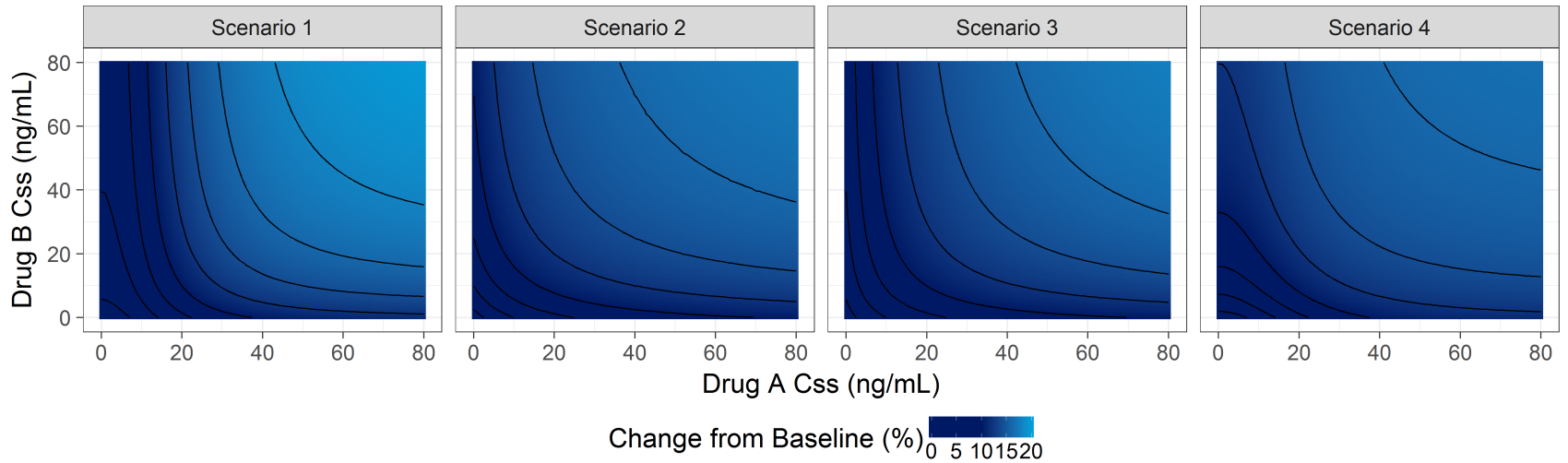
"Typical design":
3x3 factorial, doses equispaced
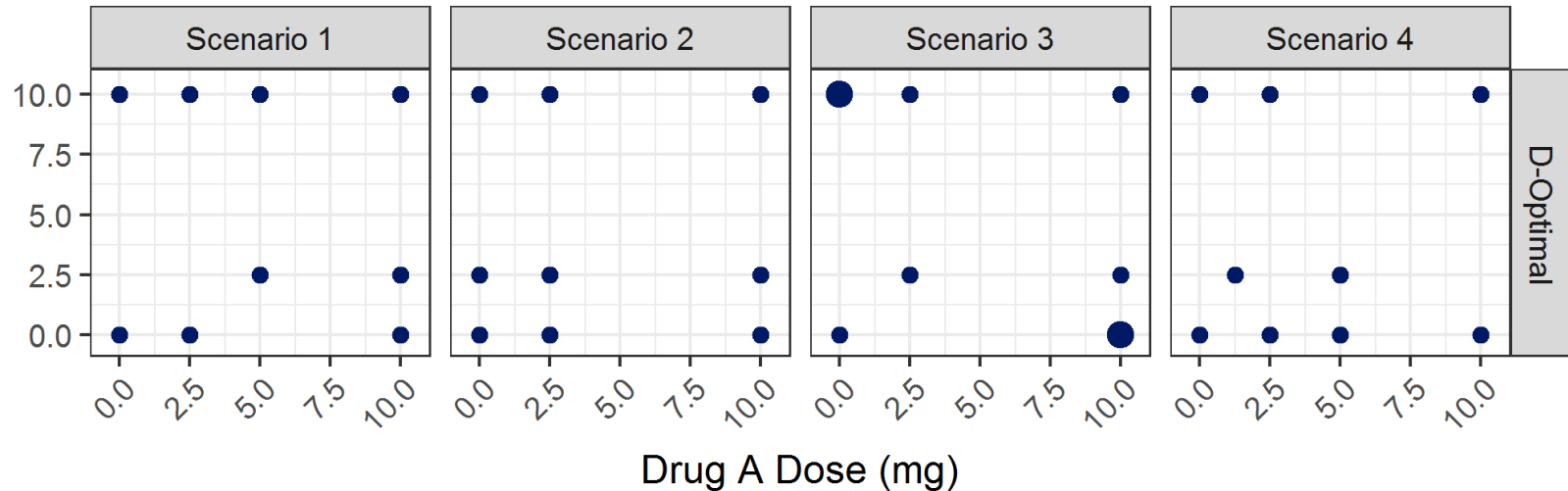
Original design
N = 60/arm

FIM prediction of average RSE for the 4 scenarios:
>1000%, 46%, 59%, >1000%

D-optimized 3x3 designs

Local Optimal Designs

Note: Same weights (i.e. N/arm) for all doses: N = 60/arm, Some arms are replicates

Dose.AB • 60 • 120 ● 180 ● 240 ● 300

FIM prediction of average RSE for the 4 scenarios:
42%, 33%, 49%, 39%

Uncertainty in model and parameter space?

- ## Expectation (E) designs: E(ln(det(FIM))
  - Dodds *et al.,* Robust Population Pharmacokinetic Experiment Design. *Journal of Pharmacokinetics and Pharmacodynamics,* 2005*.*

- ## Model based adaptive optimal design
  - Pierrillas *et al*., Model-Based Adaptive Optimal Design (MBAOD) Improves Combination Dose Finding Designs: an Example in Oncology. *The AAPS Journal,* 2018*.*
  - Strömberg, *et al*., The effect of using a robust optimality criterion in model based adaptive optimization. *Journal of Pharmacokinetics and Pharmacodynamics*, 2017.

- ## Model averaging
  - Aoki, Y., *et al*., Model selection and averaging of nonlinear mixed-effect models for robust phase III dose selection. *Journal of Pharmacokinetics and Pharmacodynamics*, 2017.

ED-optimal designs

Typical and Globally Optimal Designs

D efficiency for the ED design
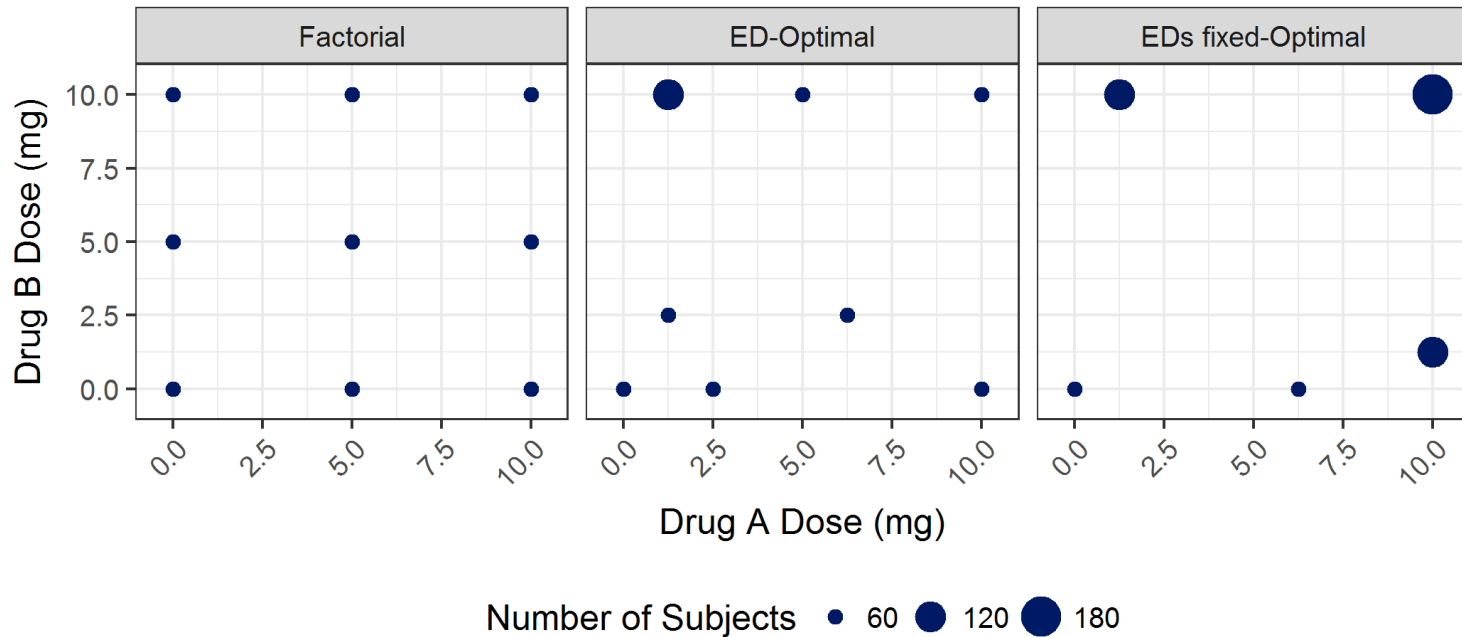
| Scenario	Eff_D
1	1.09
2	1.26
3	1.4
4	1.00

For the ED-optimal design
N/arm = 170 if RSE<30% is needed for
all parameters
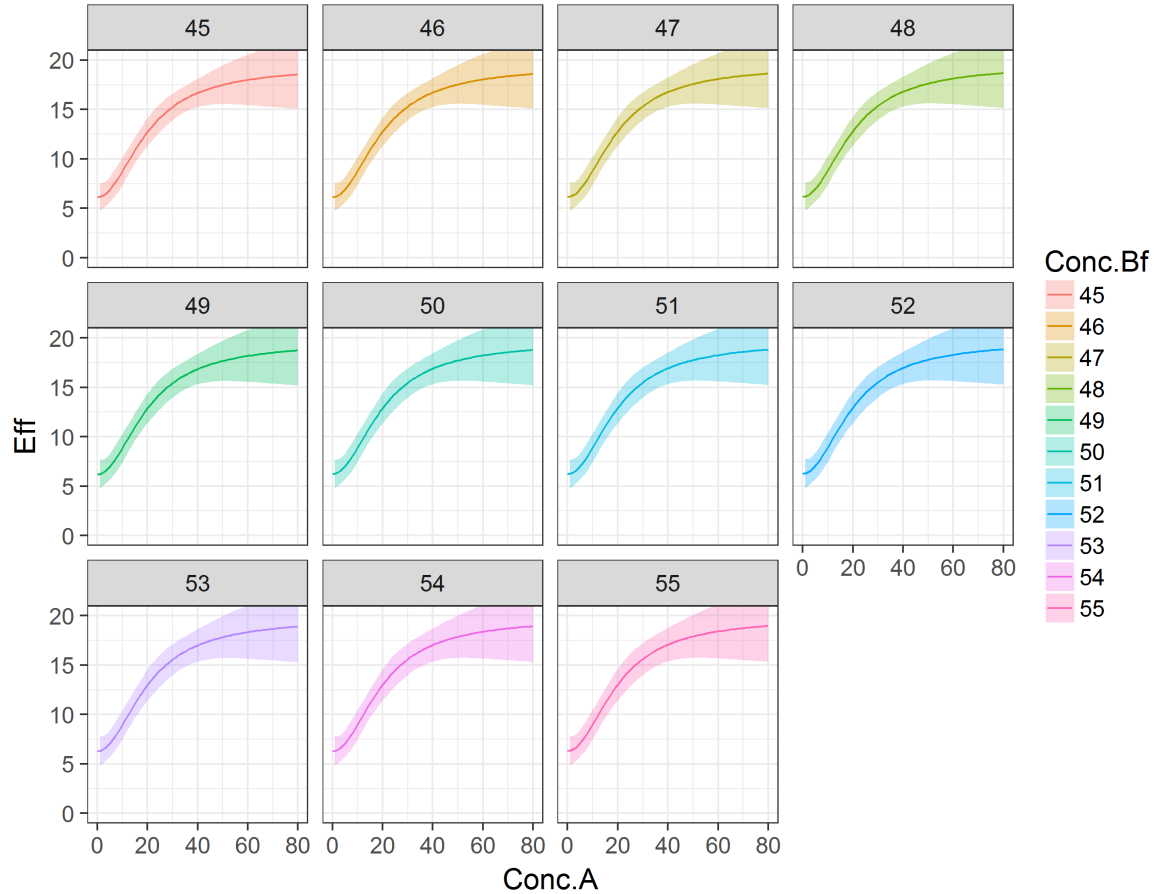
Correct dose identification

Best dose defined as the *smallest* combination of both drugs leading to a wanted effect

Steps:

- Predict DER isobole of interest from estimated parameter vector (with parameter uncertainty)

- Identify the combination of doses that minimizes the distance from the origin
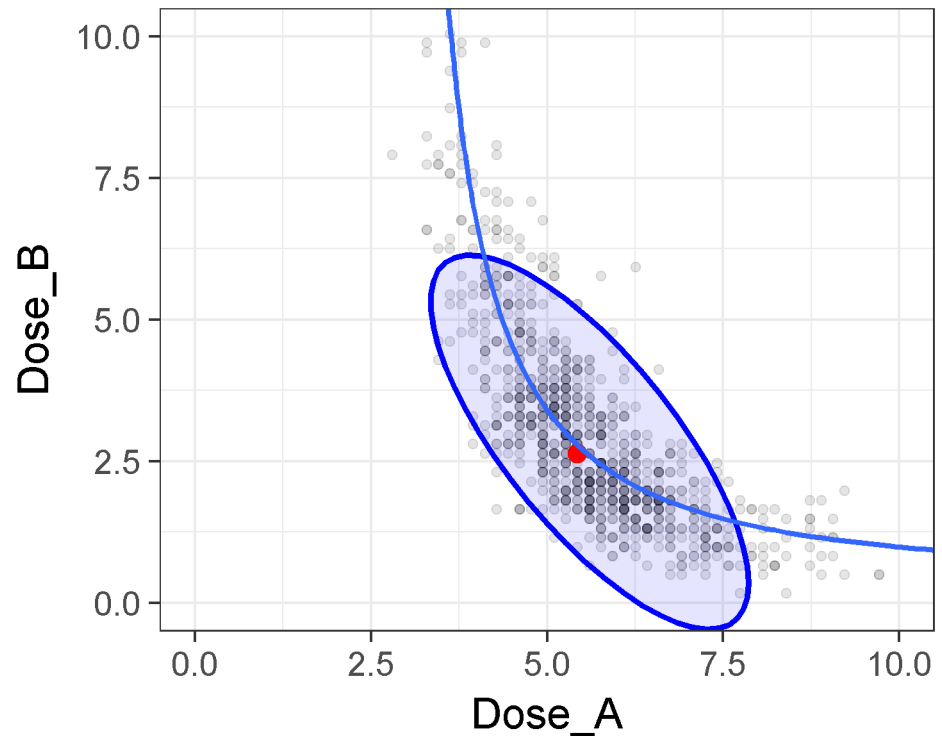
D-optimal designs: Drug A perspective

Can we do better?

Taylor & Francis
Taylor & Francis Group

OPTIMAL DESIGNS FOR ESTIMATING THE INTERESTING PART OF A DOSE-EFFECT CURVE

Frank Miller and Olivier Guilbaud

Clinical Information Science, AstraZeneca, Södertälje, Sweden

Holger Dette

Fakultät für Mathematik, Ruhr-Universität Bochum, Germany

We consider a dose-finding trial in phase IIB of drug development. For choosing an appropriate design for this trial the specification of two points is critical: an appropriate model for describing the dose-effect relationship, and the specification of the aims of the trial (objectives), which will be the focus in the present paper.

For many situations it is essential to have a robust trial objective that has little risk of changing during the complete trial due to external information. An important and realistic objective of a dose-finding trial is to obtain precise information about key parts of the dose-effect curve. We reflect this goal in a statistical optimality criterion and derive efficient designs using optimal design theory. In particular, we determine nonadaptive Bayesian optimal designs, i.e., designs which are not changed by information obtained from an interim analysis. Compared with a traditional balanced design for this trial, it is shown that the optimal design is substantially more efficient. This implies either a gain in information, or essential savings in sample size. Further, we investigate an adaptive Bayesian optimal design that uses different optimal designs before and after an interim analysis, and we compare the adaptive with the nonadaptive Bayesian optimal design. The basic concept is illustrated using a modification of a recent AstraZeneca trial.

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$$g\big(C_{A}, C_{B}, design, \theta\big) = \left(\frac{\partial E(c_{A}, c_{B})}{\partial \theta}\right)^{\mathrm{T}} \qquad (1)$$

- Minimization of the predicted variance over a range of concentration of drug A and drug B

$$s = g^{T} FIM^{-1} g \qquad (2)$$

$$\varphi = \int_{C_{A,min}}^{C_{A,max}} \int_{C_{B,min}}^{C_{B,max}} s\big(C_{A}, C_{B}, design, \theta\big) dC_{A} dc_{B} \qquad (3)$$

- Very relevant for identifying the right dose!

phi must be minimized!

IV optimality

Integration from 40 to 60 (both A and B)
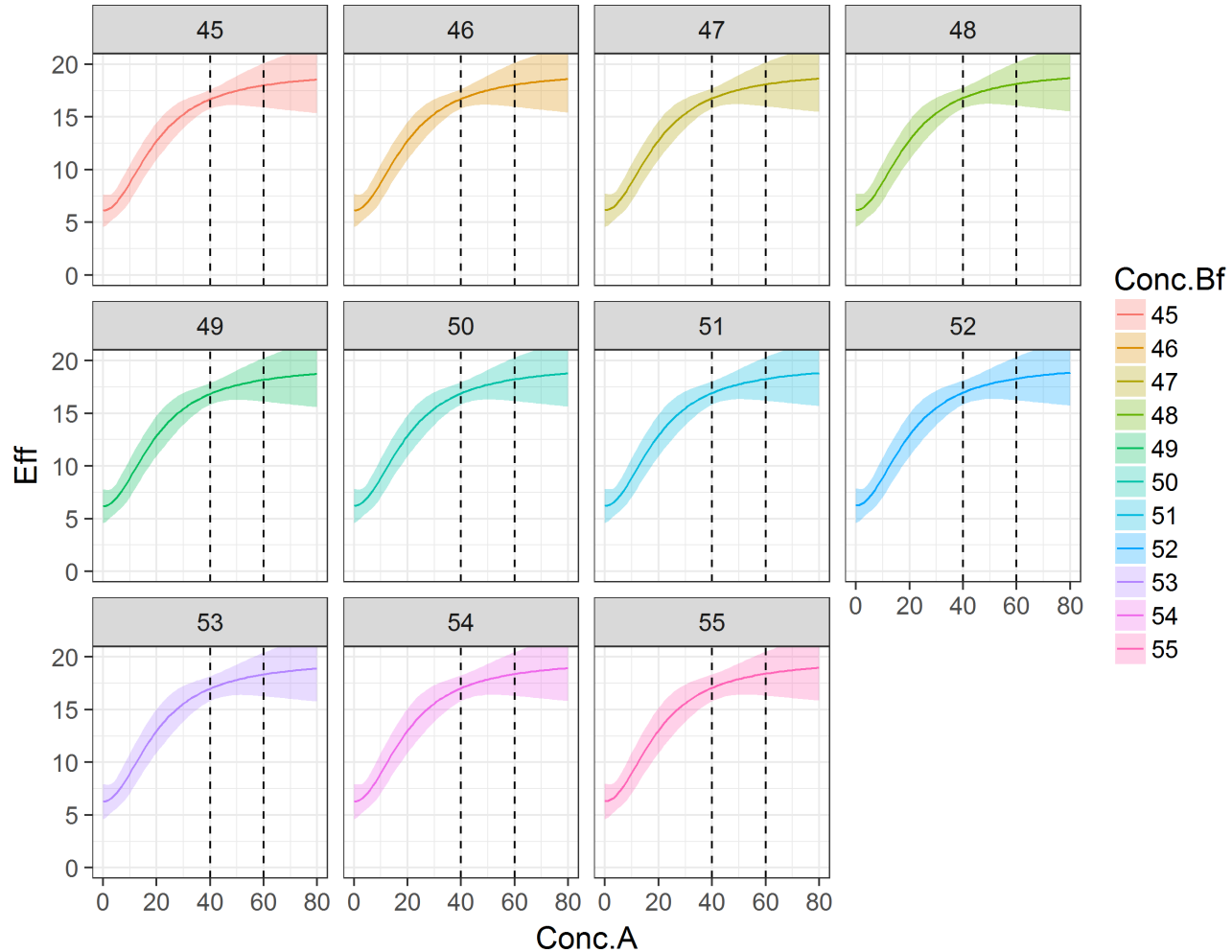

IV
Scenario 1, N=540 subjects
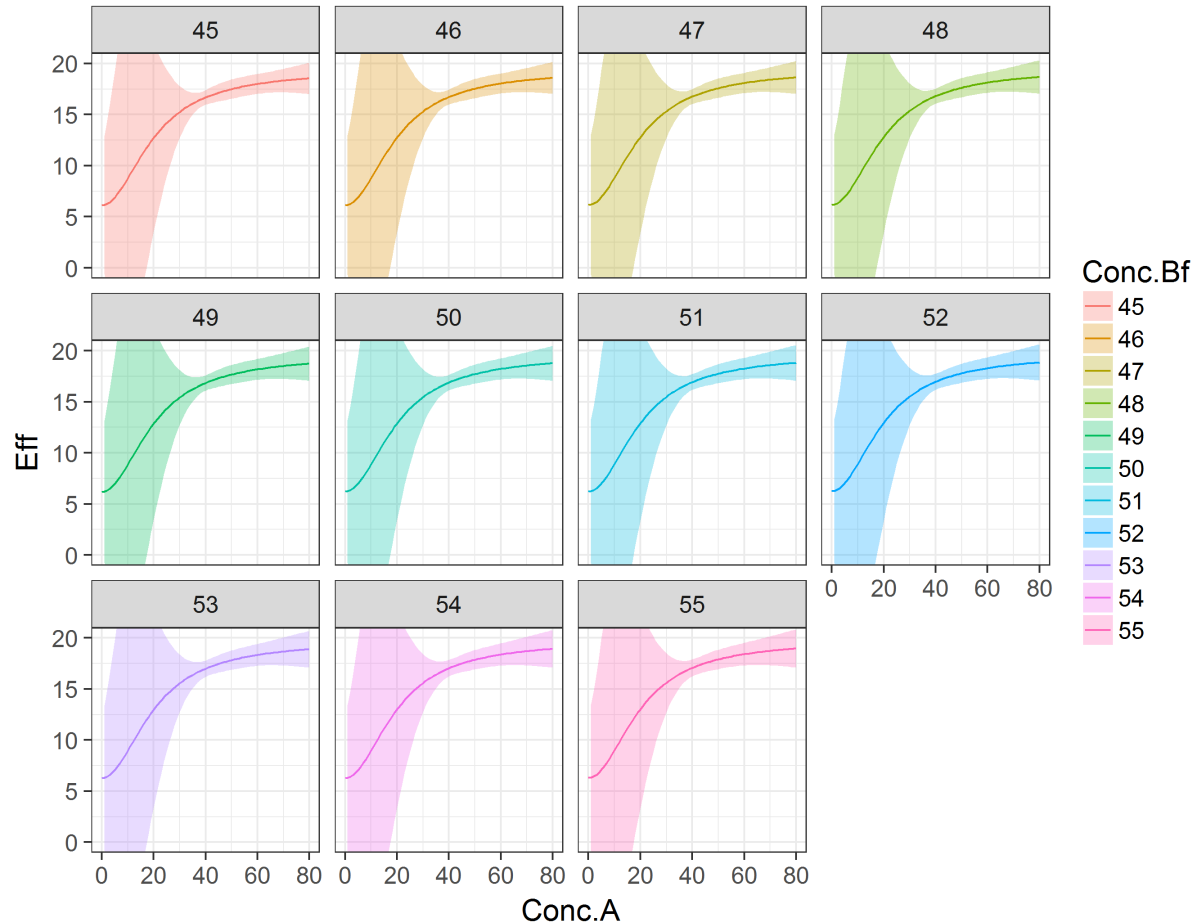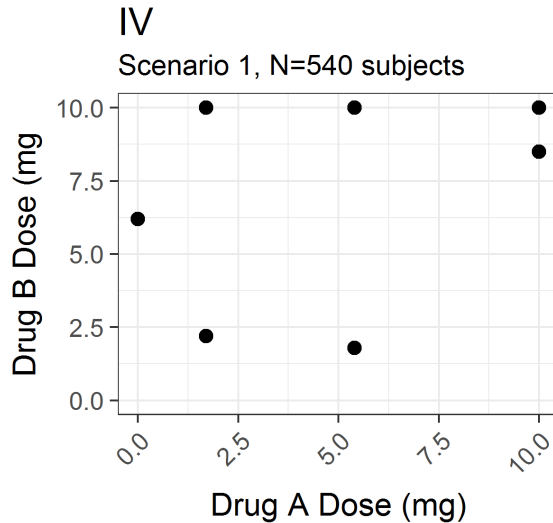
Advantages

- *Very good* prediction for a wanted area of the E-R curve

Disadvantages

- *Very large* parameter RSE (expected)
- *Implausible* clinical trial design
- Solution: A combination of D and IV
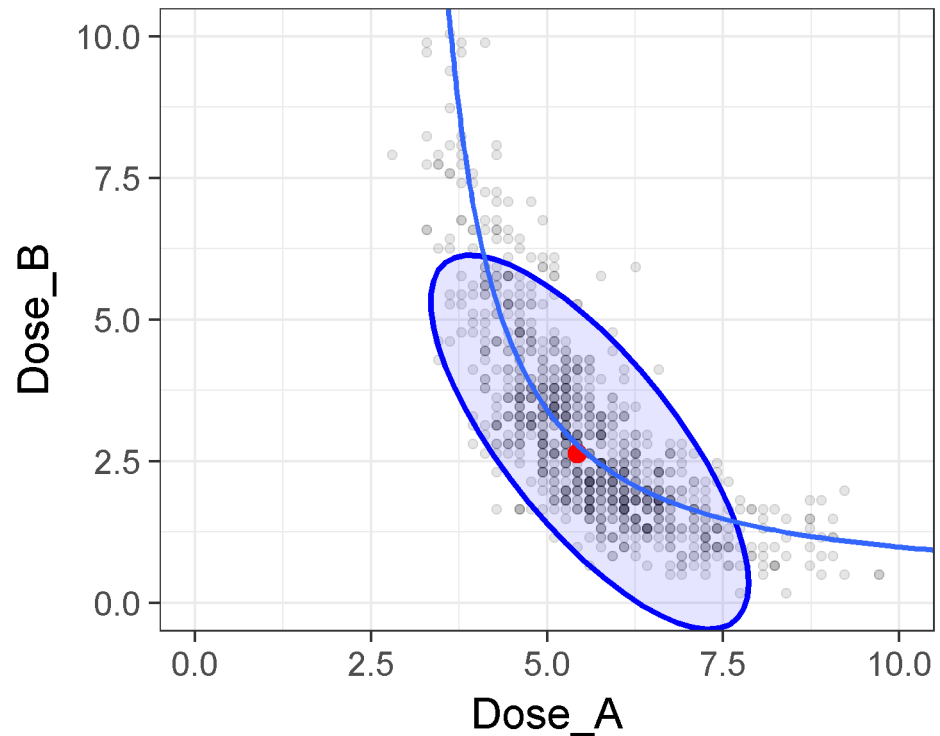
Compound D+IV
(equal weighting)

Correct dose identification

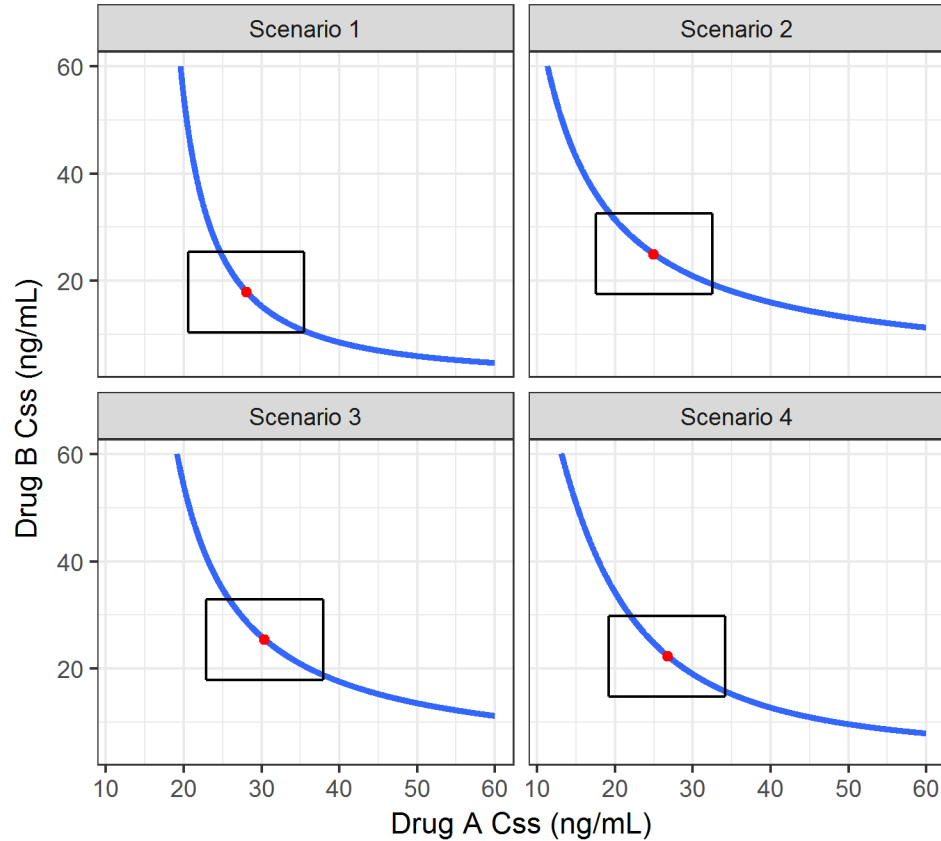Best dose defined as the *smallest* combination of both drugs leading to a wanted effect

Steps:

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Scenarios for dose identification

Target effect: 10% change from baseline (CFB)
- We have a 3% CFB for placebo
- The light blue lines represent the true 13% (10%+3%) isobole for the different scenarios
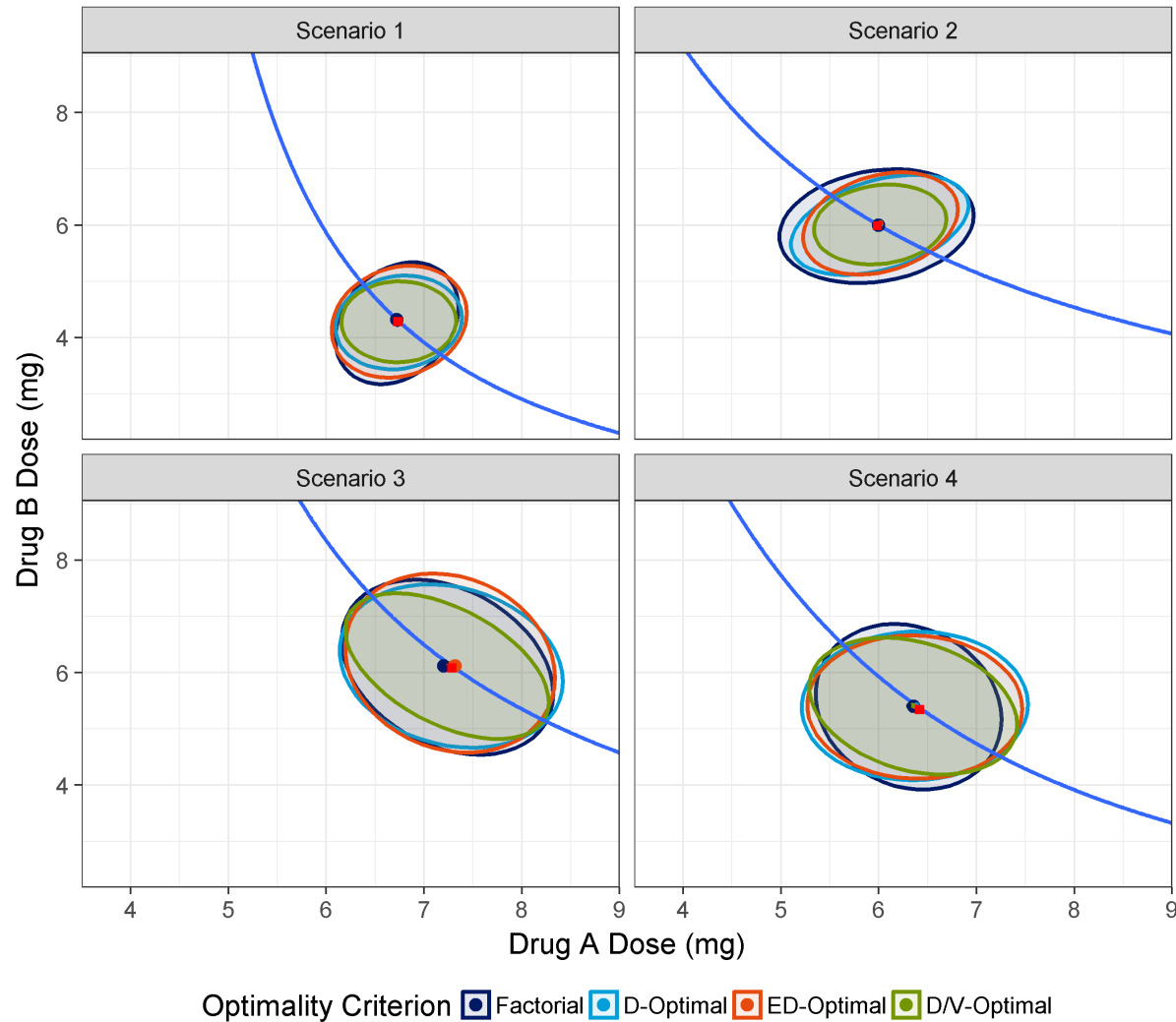
The red dot is the "optimal combination"
- Simultaneously minimizes the dose of both drugs.

The squares represent the area over which the integration for the D/V-Optimality criterion was performed
- It is a square around the "best combination dose" with a length of each side L=15 ng/mL (chosen arbitrarily)

Ability of each design to identify the true "optimal combination"
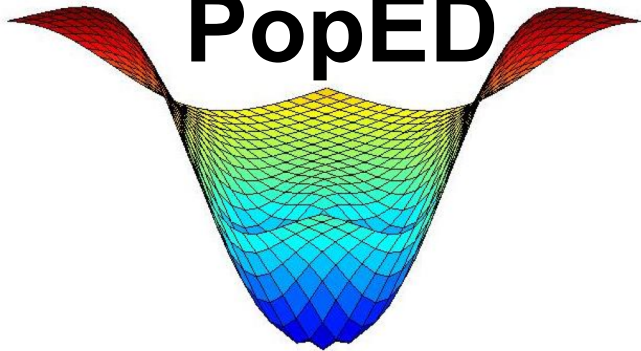
Discussion

- Compound D/IV-criterion designs are a promising way forward for dose finding in combination therapy studies

- Further comparisons with other design scenarios are needed

- Computation of E(D/IV)-designs with parameter uncertainty will be investigated

Software

PopED

poped.sf.net

https://github.com/andrewhooker/PopED

- Optimal experimental design software
- Flexible description of models
- Flexible description of design space
- Flexible design optimization
- Robust design criteria
- Written in R (Package available via CRAN)