Implementing Optimal Designs for Dose-Response Studies through Adaptive Randomization for a Small Population Group

Yevgen Ryeznik[1,2], Oleksandr Sverdlov[3], Andrew C. Hooker[2]

[1]Department of Mathematics, Uppsala University

[2]Department of Pharmaceutical Biosciences, Uppsala University

[3]Novartis Institutes for BioMedical Research

PODE 2017

Outline

1. Motivation
2. Randomization targeting (un)equal allocation
3. Simulation study
4. Summary

UPPSALA UNIVERSITET

Outline

1. Motivation
2. Randomization targeting (un)equal allocation
3. Simulation study
4. Summary

Accelerated Failure Time (AFT) Model

Let $T > 0$ be a time-to-event variable:

$$T \sim Weibull(\lambda, p).$$

We consider the following AFT model with a single covariate x:

$$\log T = \beta_0 + \beta_1 x + \beta_2 x^2 + b\varepsilon,$$

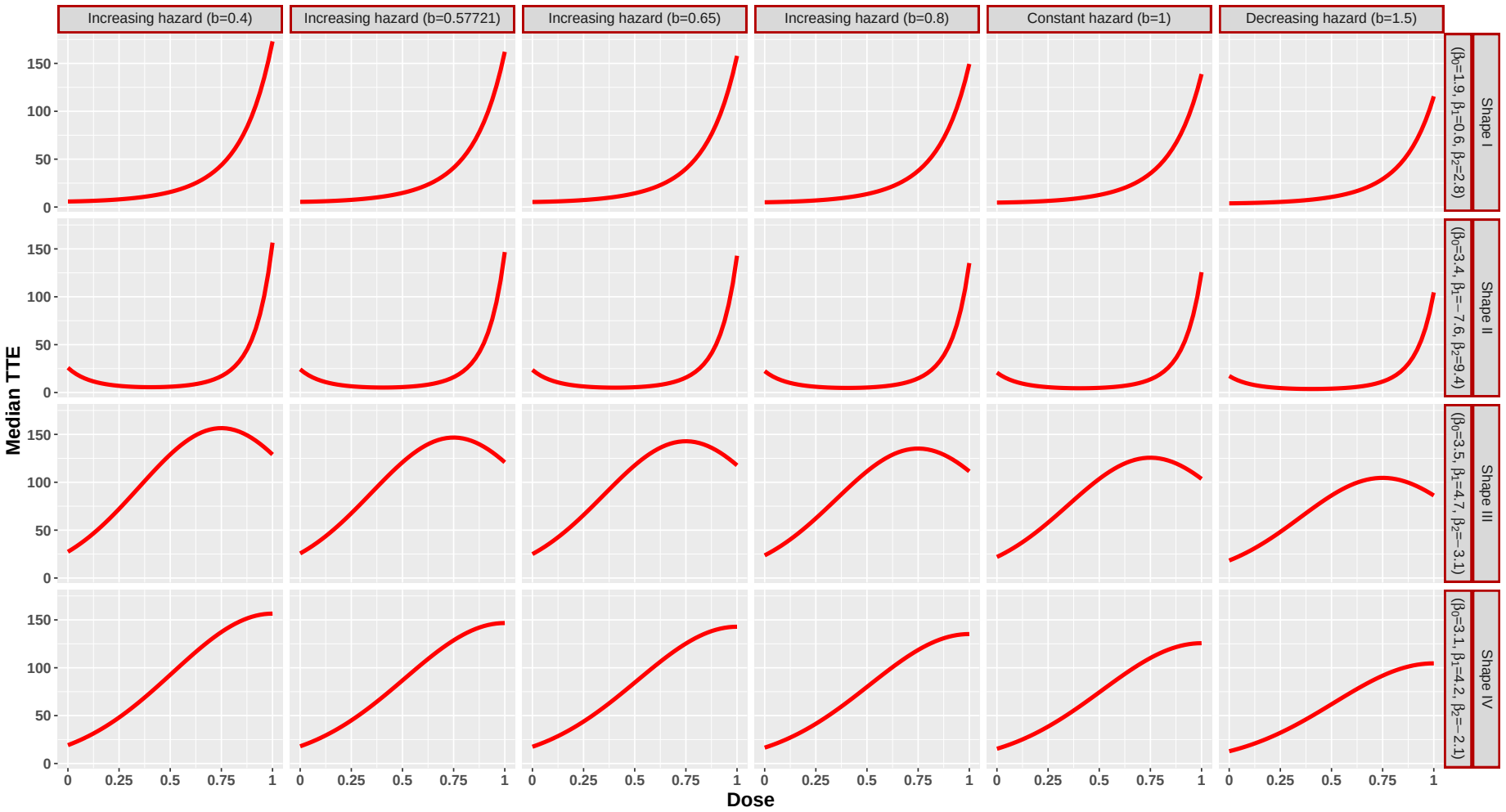
where

- x corresponds to a dose (treatment arm),
- scale parameter: $\lambda = \exp(\beta_0 + \beta_1 x + \beta_2 x^2)$,
- shape parameter: $p = b^{-1}$,
- and $\varepsilon \sim f_\varepsilon(v) = \exp(v - \exp(v))$ – *extreme value distribution.*

UPPSALA UNIVERSITET

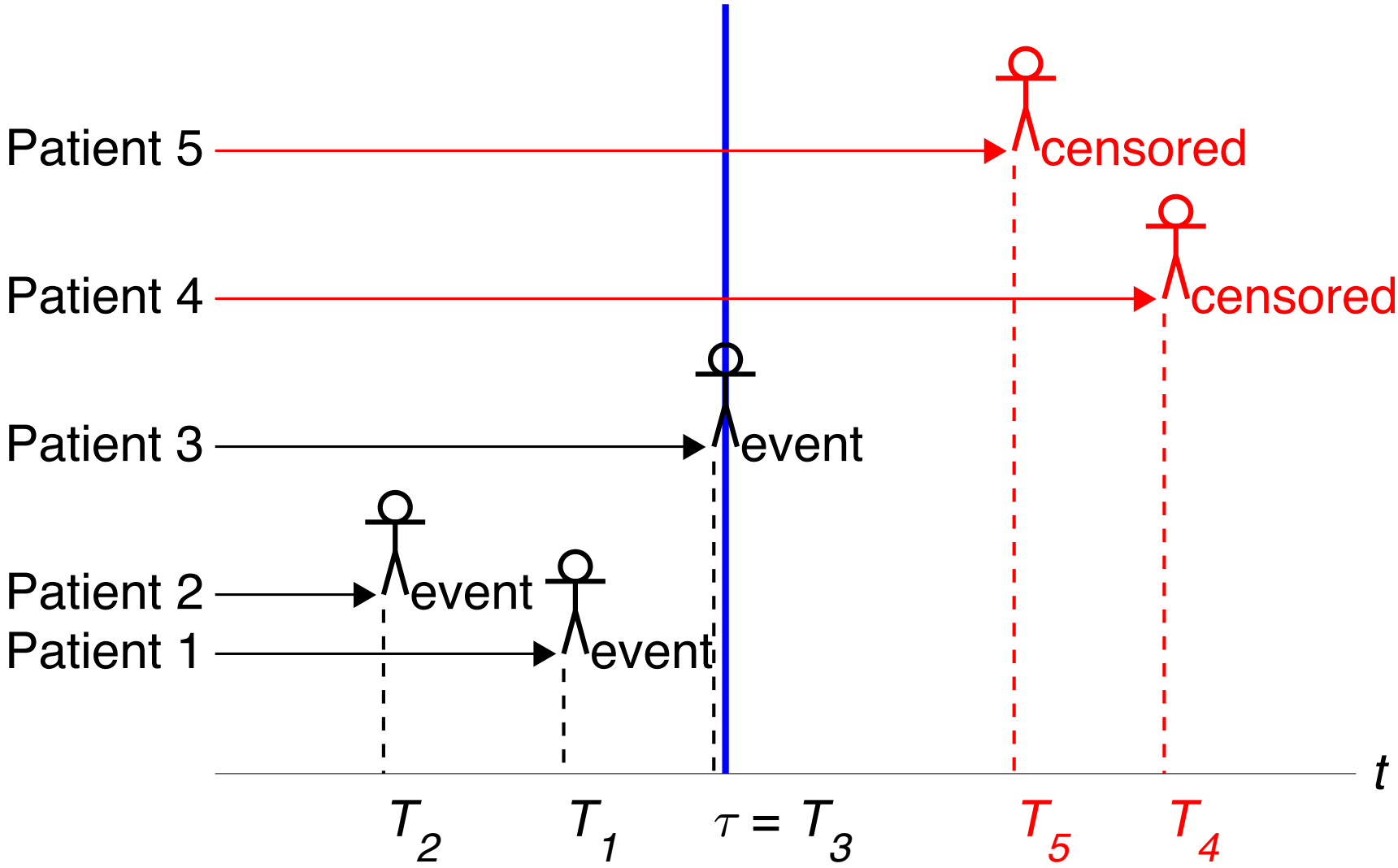
Accelerated Failure Time (AFT) Model

Dose-response relashionship: $Median(T|x) = \exp(\beta_0 + \beta_1 x + \beta_2 x^2)\{\log(2)\}^b$



UPPSALA UNIVERSITET

Censoring



UPPSALA UNIVERSITET

Likelihood and Fisher Information

- For a sample of n patients and a vector of parameters $\boldsymbol{\theta} = (\boldsymbol{\beta}^{\mathrm{T}}, b)^{\mathrm{T}}$ one can calculate log-*likelihood function* $\log \mathcal{L}(\boldsymbol{\theta})$.
- Then, *MLE*s of unknown model parameters $(\widehat{\boldsymbol{\theta}}_{MLE})$ are the solutions of score equations

$$\frac{\partial \log \mathcal{L}(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}} = \begin{pmatrix} \frac{\partial \log \mathcal{L}(\boldsymbol{\theta})}{\partial \boldsymbol{\beta}} \\ \frac{\partial \log \mathcal{L}(\boldsymbol{\theta})}{\partial b} \end{pmatrix} = \mathbf{0}$$

- The corresponding *Fisher Information Matrix* is

$$I(\boldsymbol{\theta}) = -\mathbf{E}\left(\frac{\partial^2 \log \mathcal{L}(\boldsymbol{\theta})}{\partial \boldsymbol{\theta} \partial \boldsymbol{\theta}^{\mathrm{T}}}\right)$$

UPPSALA UNIVERSITET

Experimental Design

A K-points design is determined by a discrete probability measure

$$\xi = \begin{pmatrix} x_1 & x_2 & \dots & x_K \\ \rho_1 & \rho_2 & \dots & \rho_K \end{pmatrix},$$

where

- K is a number of doses (treatment arms).
- $x_1, x_2, \dots, x_K$ are selected doses.
- $\rho_1, \rho_2, \dots, \rho_K$ are proportions of subjects assigned to corresponding doses.

$$x_k \in \mathcal{X} = [0; 1], \qquad \sum_{k=1}^{K} \rho_k = 1.$$

UPPSALA UNIVERSITET

Experimental Design

A K-points design is determined by a discrete probability measure

$$\xi = \begin{pmatrix} x_1 & x_2 & \dots & x_K \\ \rho_1 & \rho_2 & \dots & \rho_K \end{pmatrix},$$

where

- K is a number of doses (treatment arms) – ***K* is to be determined**.
- $x_1, x_2, \dots, x_K$ are selected doses – **doses are to be determined**.
- $\rho_1, \rho_2, \dots, \rho_K$ are proportions of subjects assigned to corresponding doses – **proportions are to be determined**.

$$x_k \in \mathcal{X} = [0; 1], \qquad \sum_{k=1}^{K} \rho_k = 1.$$

UPPSALA UNIVERSITET

D-optimal Design

- For a given design ξ the full *Fisher Information Matrix* is

$$FIM(\xi, \boldsymbol{\theta}) = n \sum_{k=1}^{K} \rho_k I(\boldsymbol{\theta}|x_k).$$

- Then, a *D-optimal design* is determined as a solution of the following optimization problem

$$\xi_D^* = \arg\max_{\xi} |FIM(\xi, \boldsymbol{\theta})|.$$

UPPSALA UNIVERSITET

D-optimal Design

Without censoring, *D-optimal design* is a *3-points balanced (uniform) design*

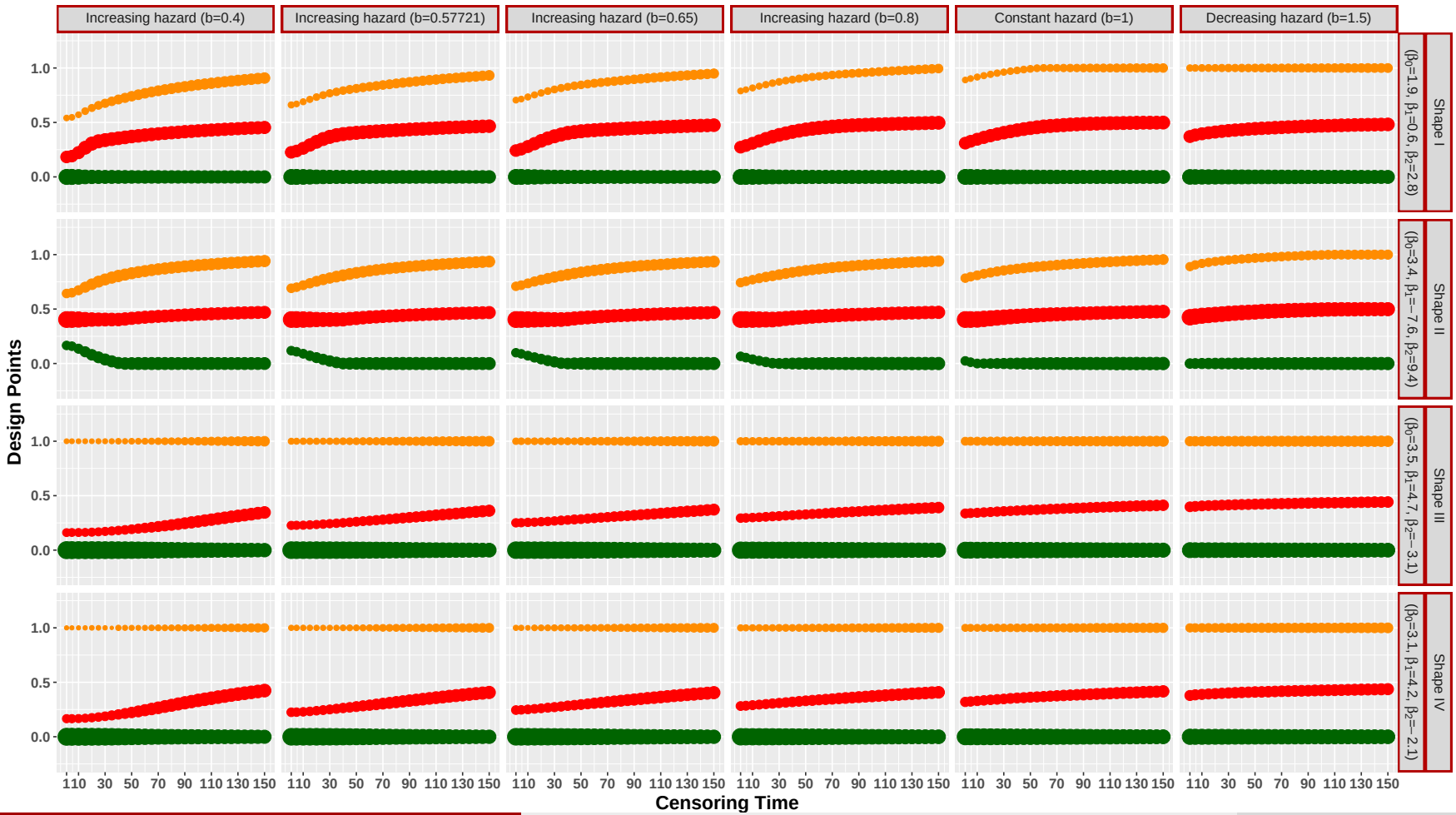
$$\begin{pmatrix} 0 & 0.5 & 1 \\ 1/3 & 1/3 & 1/3 \end{pmatrix},$$

where
$$\begin{bmatrix} 0 & - & \text{minimum dose} \\ 0.5 & - & \text{average dose} \\ 1 & - & \text{maximum dose} \end{bmatrix}$$

UPPSALA UNIVERSITET

D-optimal Design

In the presence of censoring *D-optimal design* still has 3 points but *it is shifted from the uniform design.*



Q: Given (D-)optimal design ξ^* and sample size n, how to implement it in practice, i.e. ***how to target optimal proportions*** $\rho_k^*, k = 1, 2, \ldots, K$?

UPPSALA UNIVERSITET

Q: Given (D-)optimal design ξ^* and sample size n, how to implement it in practice, i.e. ***how to target optimal proportions*** $\rho_k^*, k = 1, 2, \ldots, K$?

A: To choose a proper ***randomization procedure***!

UPPSALA UNIVERSITET

Outline

1. Motivation
2. Randomization targeting (un)equal allocation
3. Simulation study
4. Summary

UPPSALA UNIVERSITET

Requirements for a "Good" Randomization Procedure

- **Balance**
  - Treatment group sizes should be very close to the desired target allocation ratio, ***throughout the course of the trial***
- **Randomness**
  - The procedure should have low proportion of deterministic assignments to minimize chance of selection bias
- **Known statistical properties**
  - The procedure should have ***established statistical properties*** and should lead to ***valid statistical inference*** at the end of the trial
- **Ease of implementation**

UPPSALA UNIVERSITET

Notations used

K	Number of treatment arms ($K \geq 2$)
$w_1 : w_2 : \ldots : w_K$	Target allocation ratio (integers with $GCD = 1$)
$\rho_k = \frac{w_k}{\sum_{k=1}^{K} w_k}$	Target allocation proportions ($0 < \rho_k < 1, \sum_{k=1}^{K} \rho_k = 1$)
n	Total sample size for the trial
$N_1(j), N_2(j), \ldots, N_K(j)$	Treatment group sizes after j subjects have been randomized ($N_1(j) + N_2(j) + \ldots + N_K(j) = j$)
$P_1(j), P_2(j), \ldots, P_K(j)$	Randomization probabilities to treatments $1, 2, \ldots K$ for the $j-$th subject ($0 \leq P_k(j) \leq 1$ and $P_1(j) + P_2(j) + \ldots + P_K(j) = 1$)

UPPSALA UNIVERSITET

Example

- Design

$$\xi = \begin{pmatrix} 0 & 0.25 & 0.59 \\ 0.39 & 0.35 & 0.26 \end{pmatrix}$$

- $K = 3$ (a three-arm trial)
- $\rho_1 = 0.39$, $\rho_2 = 0.35$, $\rho_3 = 0.26$ – target allocation proportions for treatments $1, 2, 3$
- $n = 100$ – total sample size
- It is desirable to achive final sample sizes as follows:

$$N_1 = 39, N_2 = 35, N_3 = 26,$$

  i.e. target allocation ratio is

$$w_1 : w_2 : w_3 = 39 : 35 : 26$$

- It is also desirable to have $j^{-1}N_k(j) \approx \rho_k$; $k = 1, 2, 3$ throughout the trial, while maintaining the randomized nature of the experiment

UPPSALA UNIVERSITET

Randomization Procedures for Unequal Allocations

1. Completely Randomized Design – CRD
2. Permuted Block Design – PBD(b)
3. Block Urn Design – BUD(λ)
4. Mass Weighted Urn Design – MWUD(α)
5. Drop-the-Loser Rule – DL(α)
6. Doubly Adaptive Biased Coin Design – DBCD(γ)
7. Constraint Balance Randomization – MaxEnt(η) and MinQD(η)

Randomization Procedures for Unequal Allocations

1. Completely Randomized Design – CRD
2. Permuted Block Design – PBD(b)
3. Block Urn Design – BUD(λ)
4. Mass Weighted Urn Design – MWUD(α)
5. Drop-the-Loser Rule – DL(α)
6. Doubly Adaptive Biased Coin Design – DBCD(γ)
7. Constraint Balance Randomization – MaxEnt(η) and MinQD(η)

All the designs depend on a tweak parameter the choice of which is an open question!

UPPSALA UNIVERSITET

Randomization Procedures for Unequal Allocations

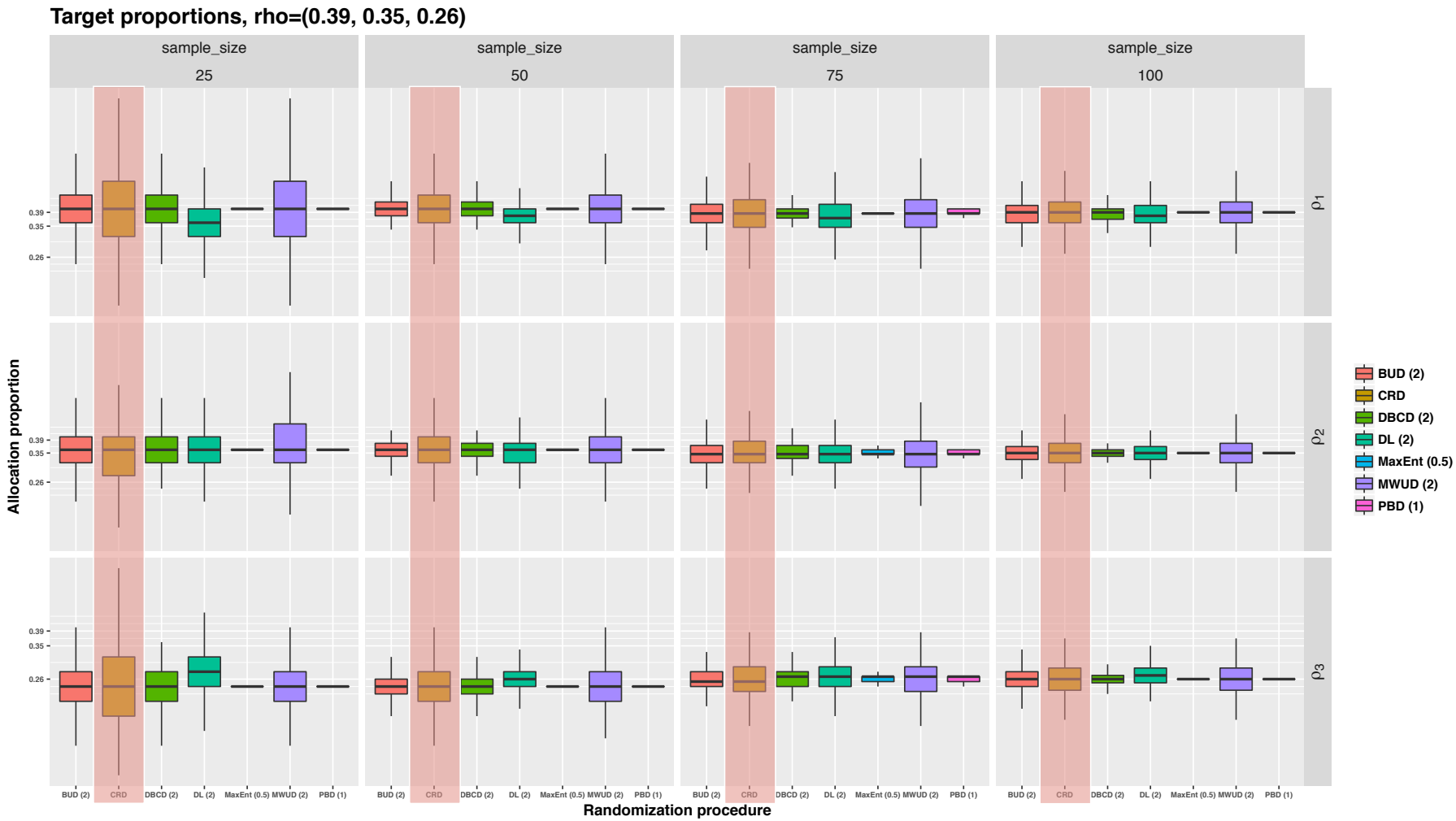
1. Zhao W, Weng Y (2011). "Block urn design. A new randomization algorithm for sequential trials with two or more treatments and balanced or unbalanced allocation". *Contemporary Clinical Trials* 32, 953-961.
2. Zhao W (2015). "Mass weighted urn design. A new randomization algorithm for unequal allocations". *Contemporary Clinical Trials* 43, 209-216.
3. Ivanova A (2003). "A play-the-winner-type urn design with reduced variability". *Metrika* 58, 1-13.
4. Hu F, Zhang LX (2004). "Asymptotic properties of doubly adaptive biased coin designs for multitreatment clinical trials". *The Annals of Statistics* 32(1), 268-301.
5. Titterington DM (1983). "On constrained balance randomization for clinical trials". *Biometrics* 39(4), 1083-1086
6. Klotz JH (1978). "Maximum entropy constrained balance randomization in clinical trials". *Biometrics* 34(2), 283-287.

Randomization Procedures for Unequal Allocations

As to our knowledge, the impact of randomization for the inference has not been considered so far!

UPPSALA UNIVERSITET

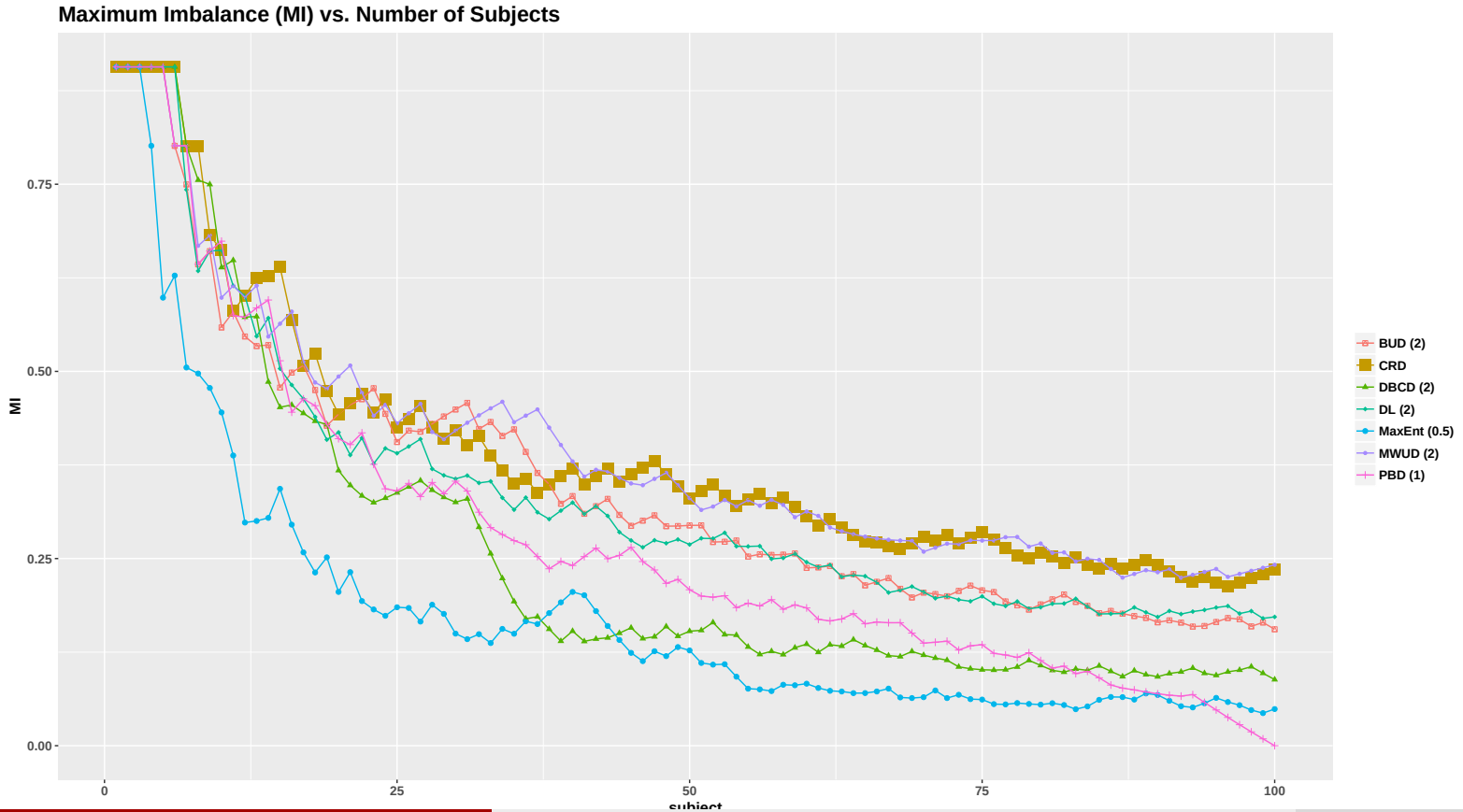
Randomization Procedures for Unequal Allocations



UPPSALA UNIVERSITET

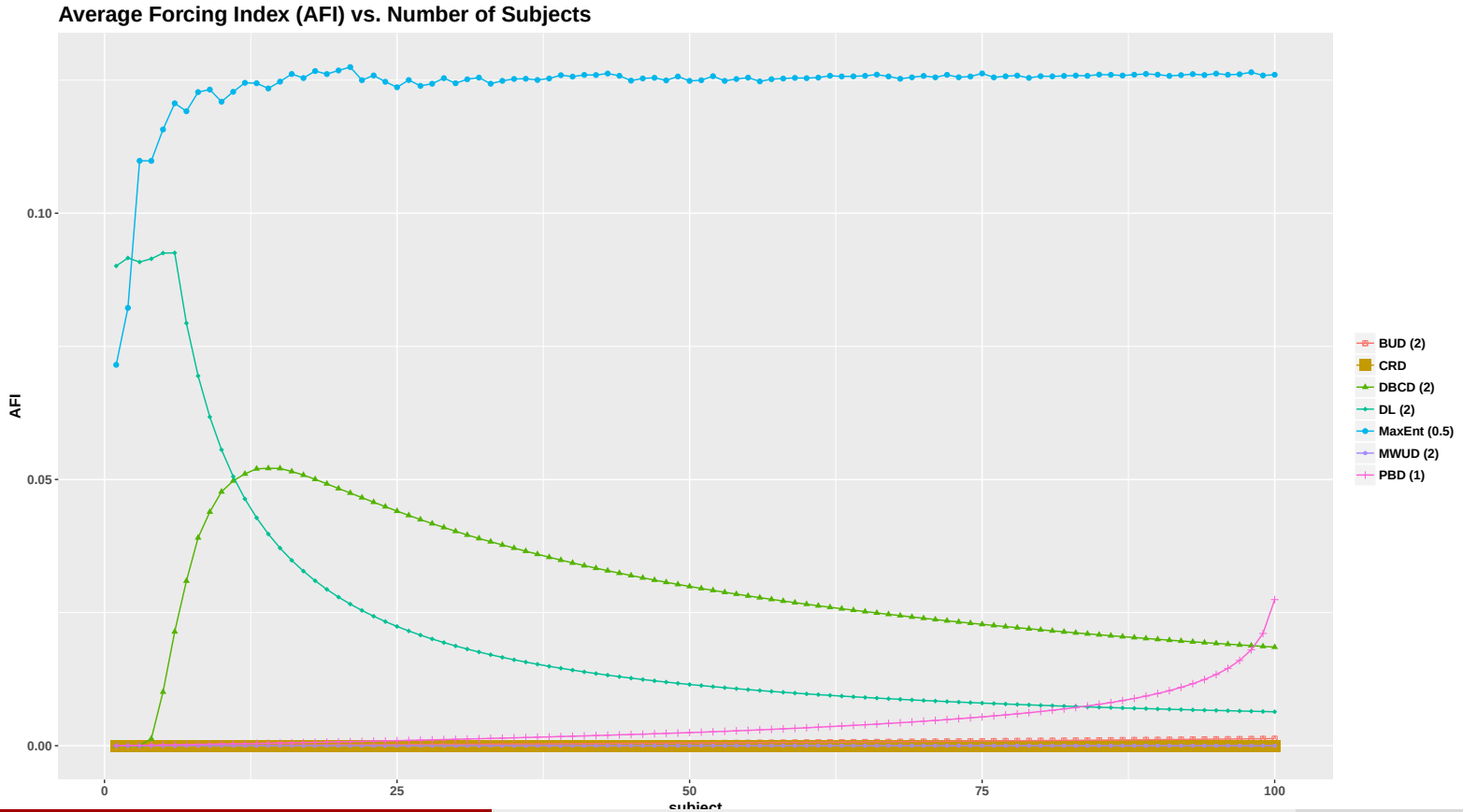
Randomization Procedures for Unequal Allocations

Imbalance: $Imb(j) = j^{-1}\sqrt{\sum_{k=1}^{K}\left(N_k(j) - j\rho_k\right)^2}, j = 1, 2, \ldots n$



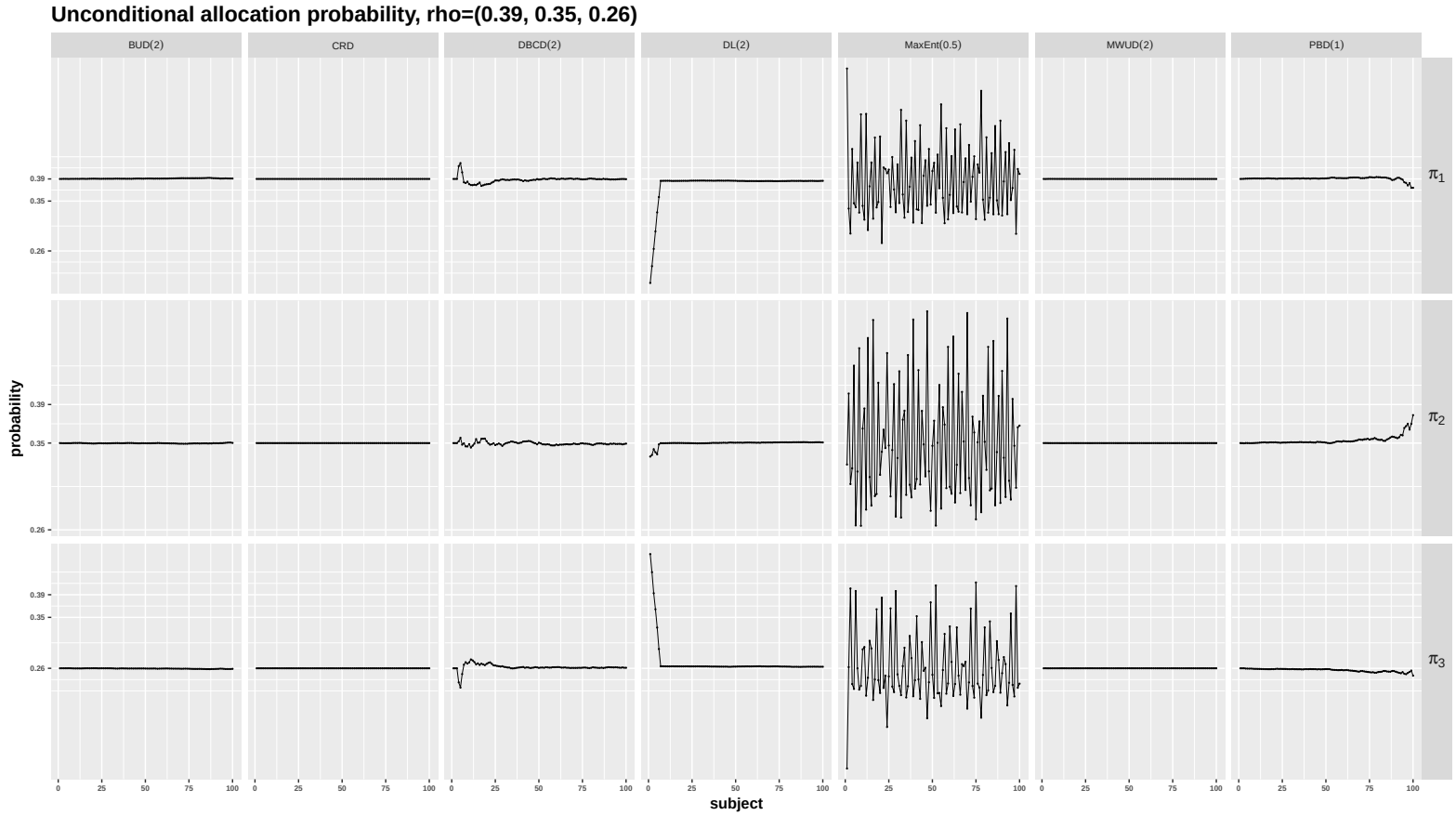
Randomization Procedures for Unequal Allocations

Forcing Index: $FI(j) = j^{-1} \sum_{i=1}^{j} \sqrt{\sum_{k=1}^{K} (P_{kj} - \rho_k)^2}, j = 1, 2, \ldots n$



Randomization Procedures for Unequal Allocations

Allocation Ratio Preserving (ARP) Property: $\mathbf{E}\left(P_{kj}\right) = \rho_k, k = 1, 2, \ldots, K.$



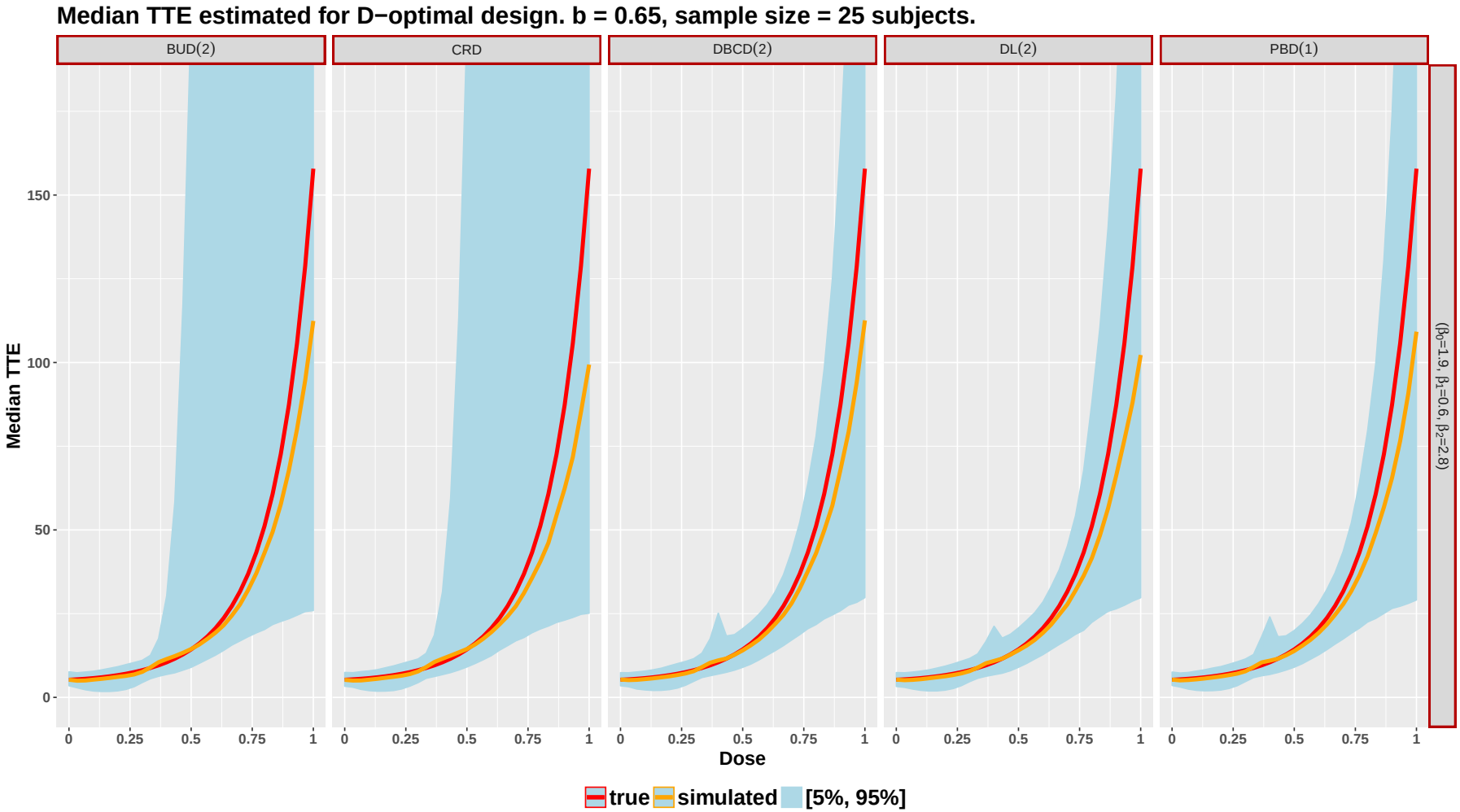
UPPSALA
UNIVERSITET

Outline

1. Motivation
2. Randomization targeting (un)equal allocation
3. Simulation study
4. Summary

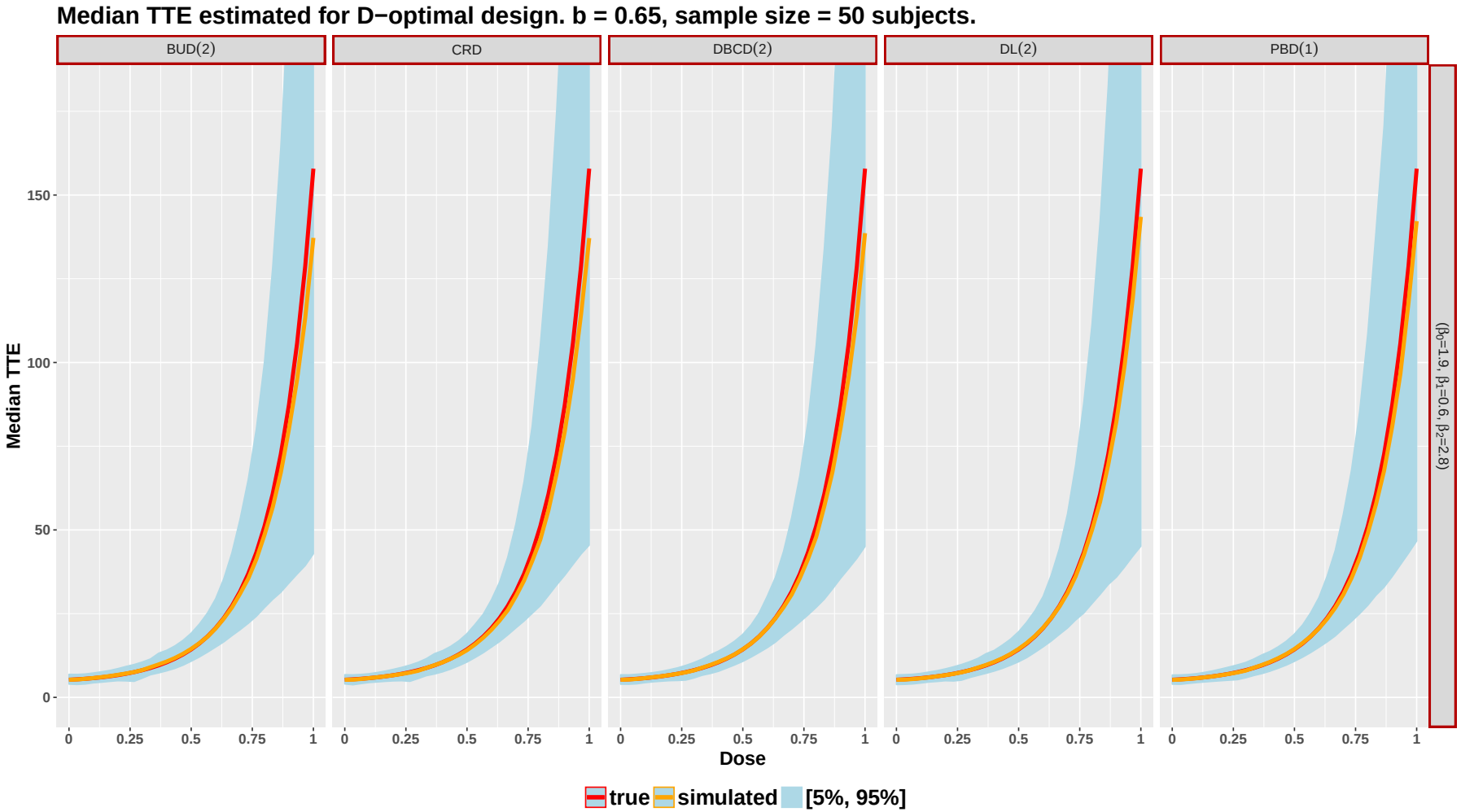
UPPSALA UNIVERSITET

Fixed D-optimal Design



UPPSALA UNIVERSITET

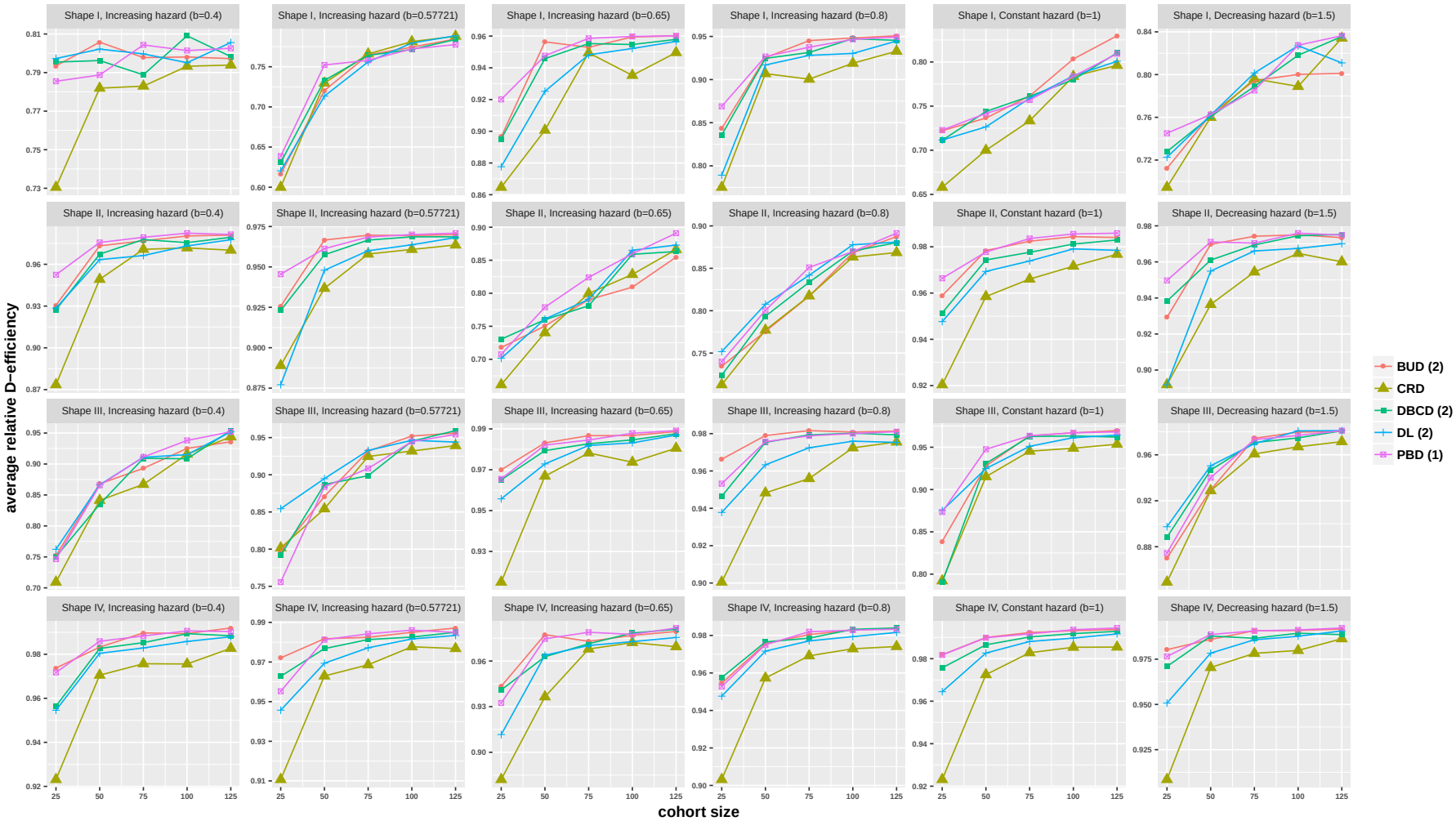
Fixed D-optimal Design



UPPSALA UNIVERSITET

Two-stage Adaptive D-optimal Design

Average relative $D-$eficiency: $RelEff = \left(\frac{|FIM(\xi^{(2)}, \boldsymbol{\theta})|}{|FIM(\xi^{*}, \boldsymbol{\theta})|} \right)^{1/4}$



UPPSALA UNIVERSITET

Outline

1. Motivation
2. Randomization targeting (un)equal allocation
3. Simulation study
4. Summary

UPPSALA UNIVERSITET

Summary

- Different randomization procedures have been considered for implementation of D-optimal design for dose-finding studies with TTE outcomes.
- The choice of randomization procedure can be important for implementation of experimental design.
- When the model parameters are known, then the estimation of dose-response curve can be too uncertain when a sample size is small.
- When the model parameters are unknown two-stage adaptive design has been considered. The efficiency of a 2nd stage design may depend on the randomization procedure in the first stage.

Thank You!