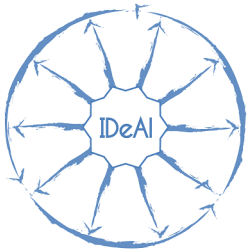
Incorporation of external information with Bayesian and frequentist methods

or

what we can talk about in the coffee room

Gerald Hlavin

IDeAl Young Scientist Meeting
Vienna, 30th June 2014



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Coffee No. 1
Bayesian Statistics

what I am doing right now

Description of Work - Task 4.1.:

“Development of evidence levels for small population groups”

the main problem

Full study programs
in **paediatric populations**
are often ***not possible***
due to **small sample-sizes**.

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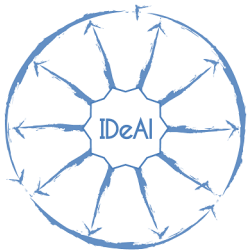
the main problem

It is necessary to

- either **raise Type I error rate**,
- or **lower** the **Power**.

the solution

- **Adult evidence** on efficacy may be **available**.
- Construction of a **Bayesian model.**
- **Translation** of frequentist methods.



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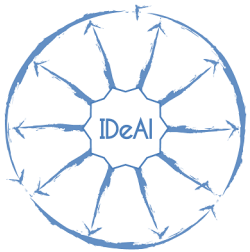
the solution

Bayesian model

- mathematically straightforward
- but
  - **How much** evidence can be **extrapolated**?
  - **Interpretability**!



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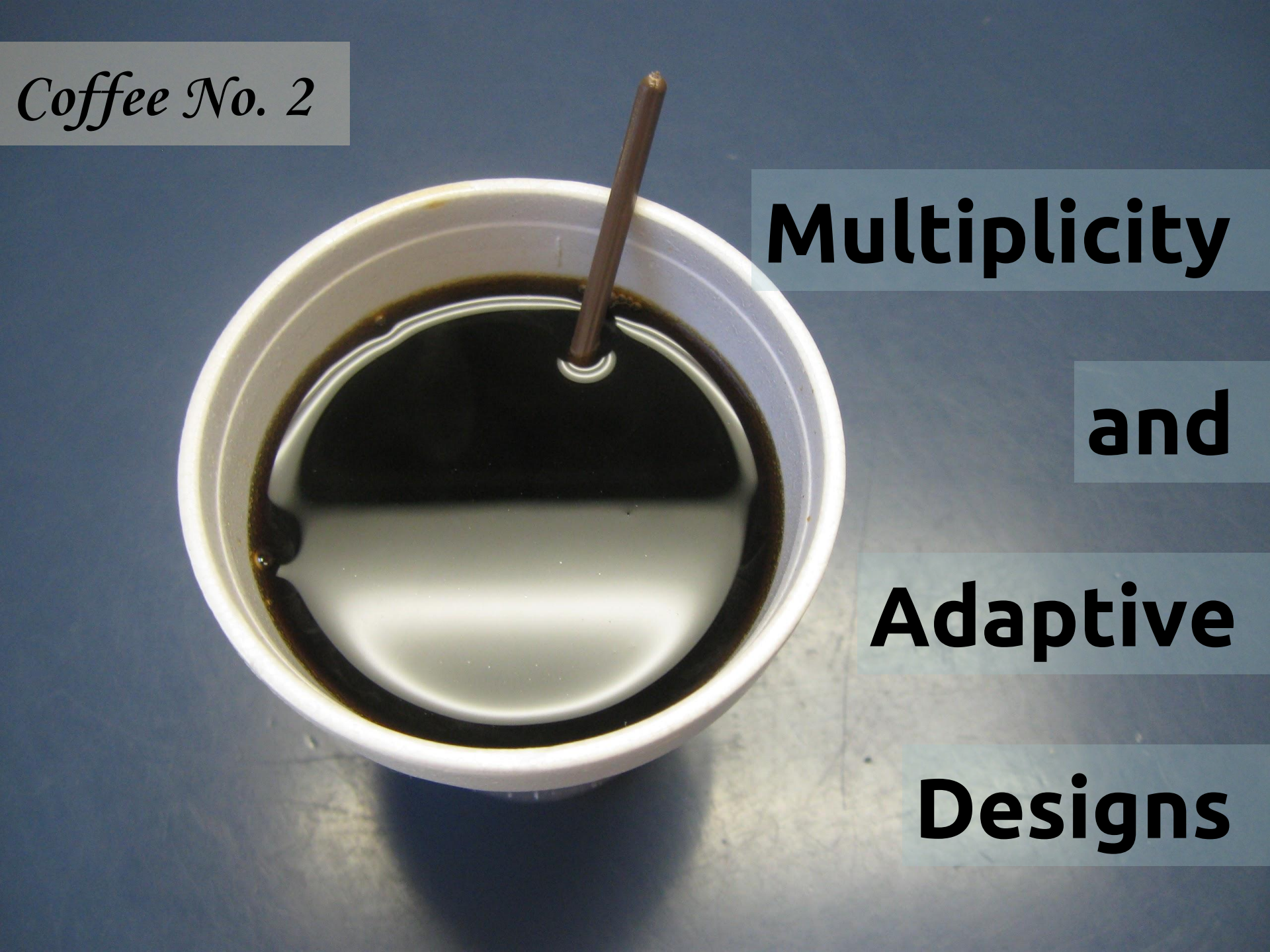
the solution

Definition of an **extrapolation probability** in a **hierarchical model.**


Coffee No. 2
Multiplicity
and
Adaptive
Designs

what I may do in the future

Description of Work - Task 4.3.:

"Adaptive designs to enable comparative effectiveness analysis"

what I may do in the future

Adaptive Designs

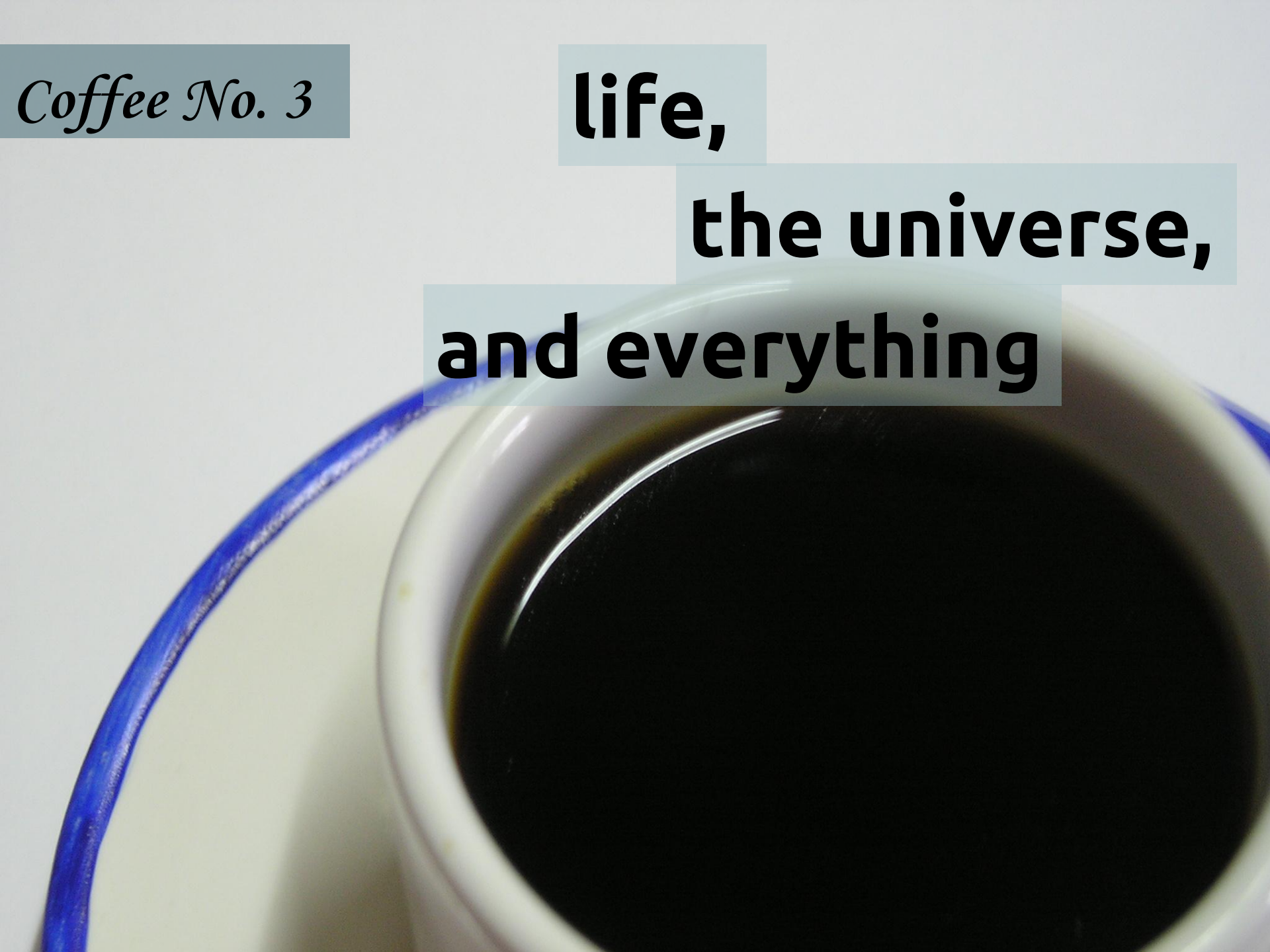
- guarantee for Type I error rate control, while
- allowing for modifying sample-sizes, hypotheses, …
- at interim

what I may do in the future

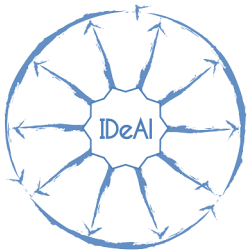
Key research topic at our section!

Coffee No. 3

life,
the universe,
and everything



Thank you!



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MCPMod approach and its further possible extensions

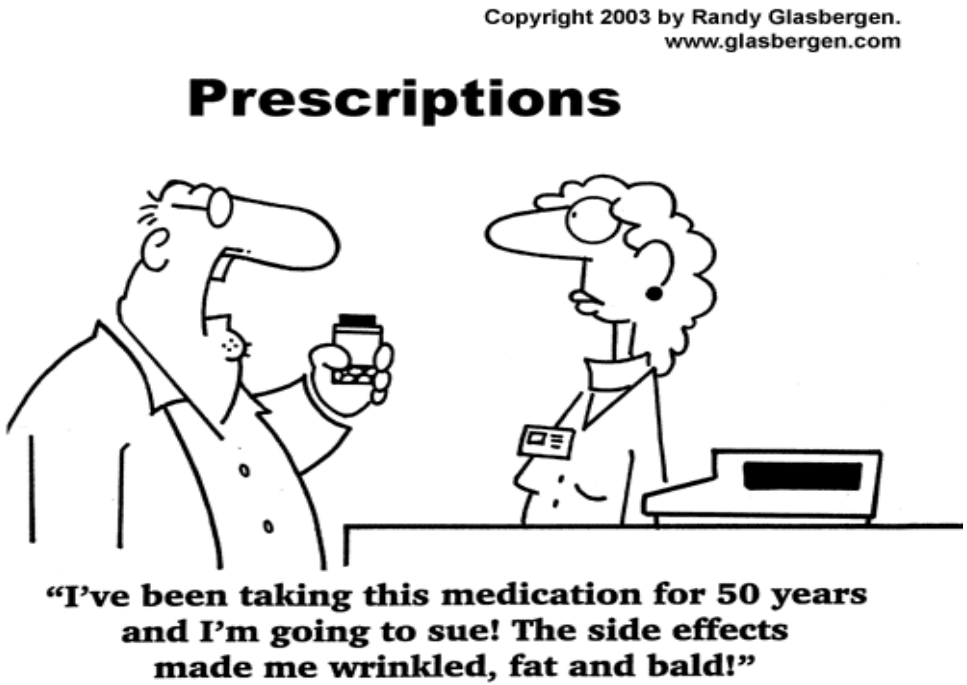
Sergii Krasnozhon

Section of Medical Statistics
The Medical University of Vienna

June 30, 2014

Introduction

- A good understanding and characterization of the **dose response relationship** is a **fundamental** step in the investigation of the new compound.



Hybrid aprroach - MCP-Mod (Bretz et al. [2005])

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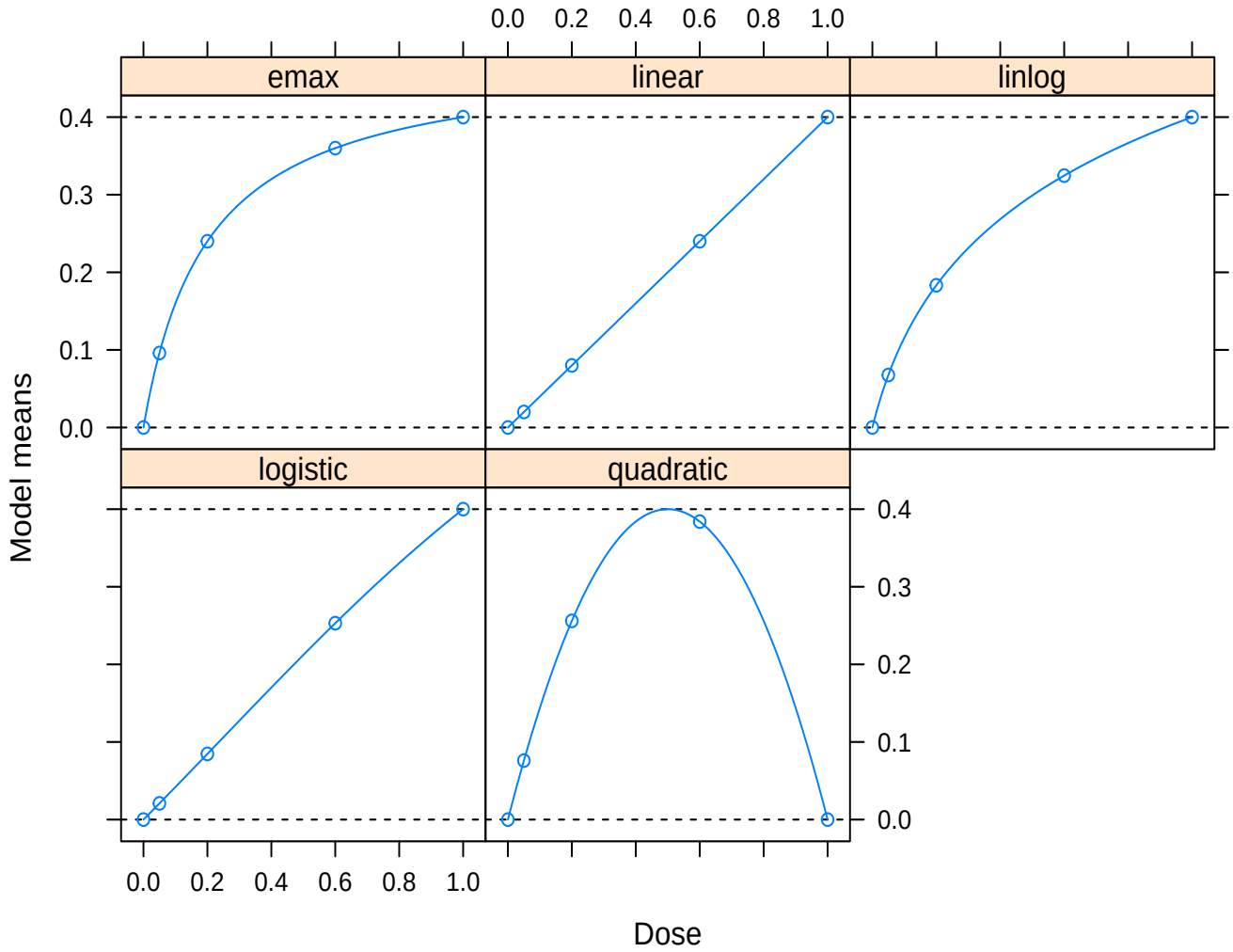
Set of **candidate models**.

Hybrid aprroach - MCP-Mod (Bretz et al. [2005])



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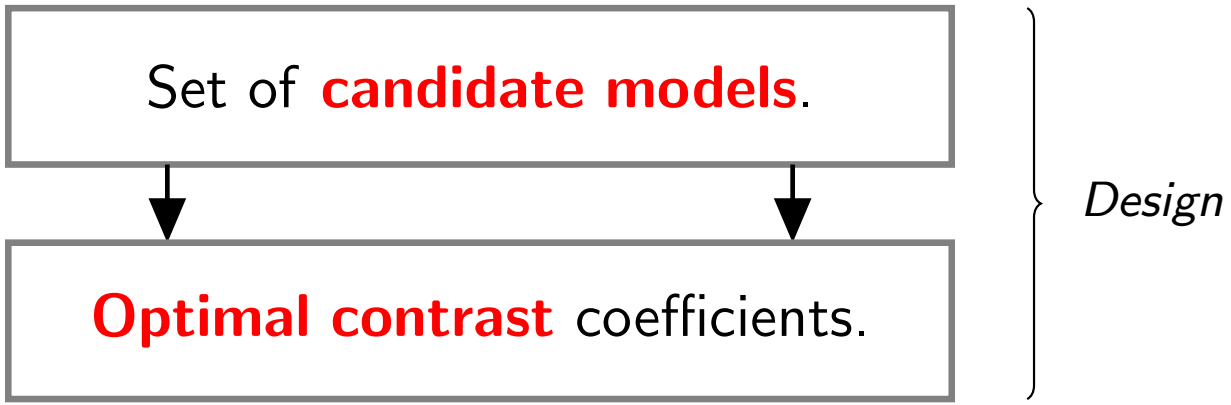
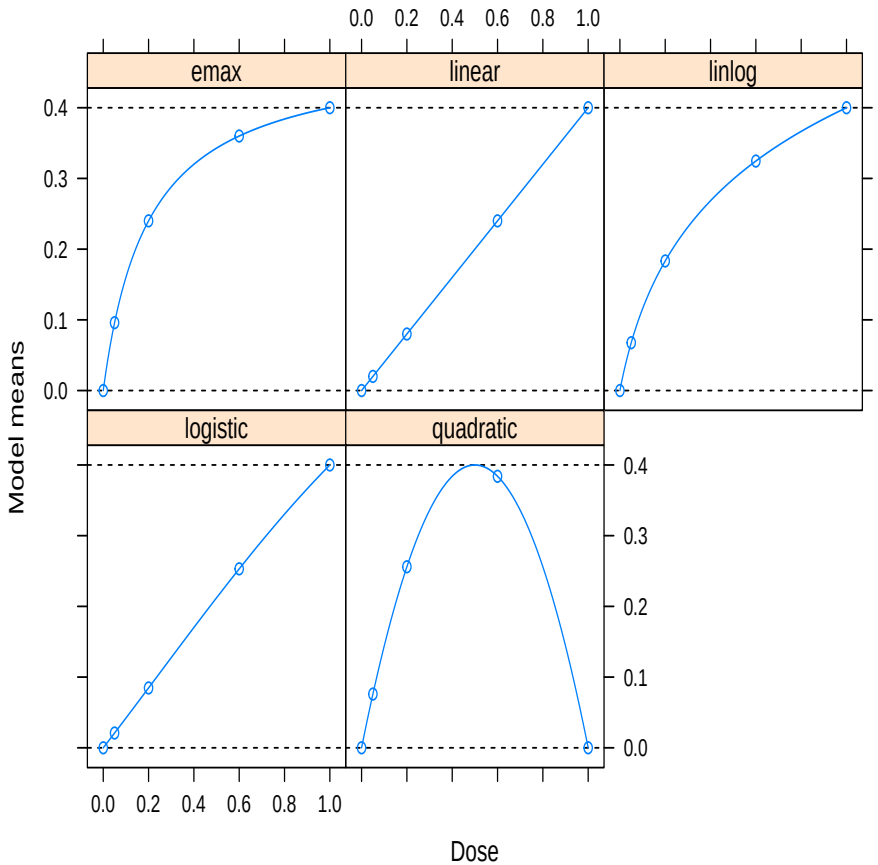
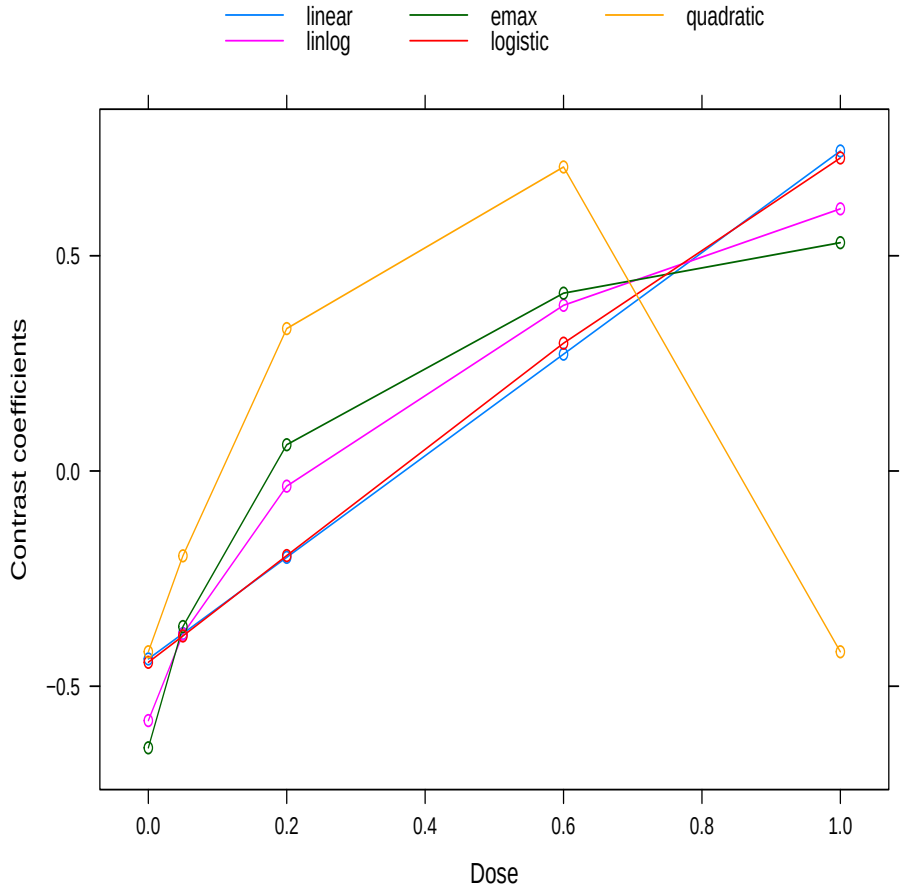


Hybrid aprroach - MCP-Mod (Bretz et al. [2005])

- The **optimal contrasts**





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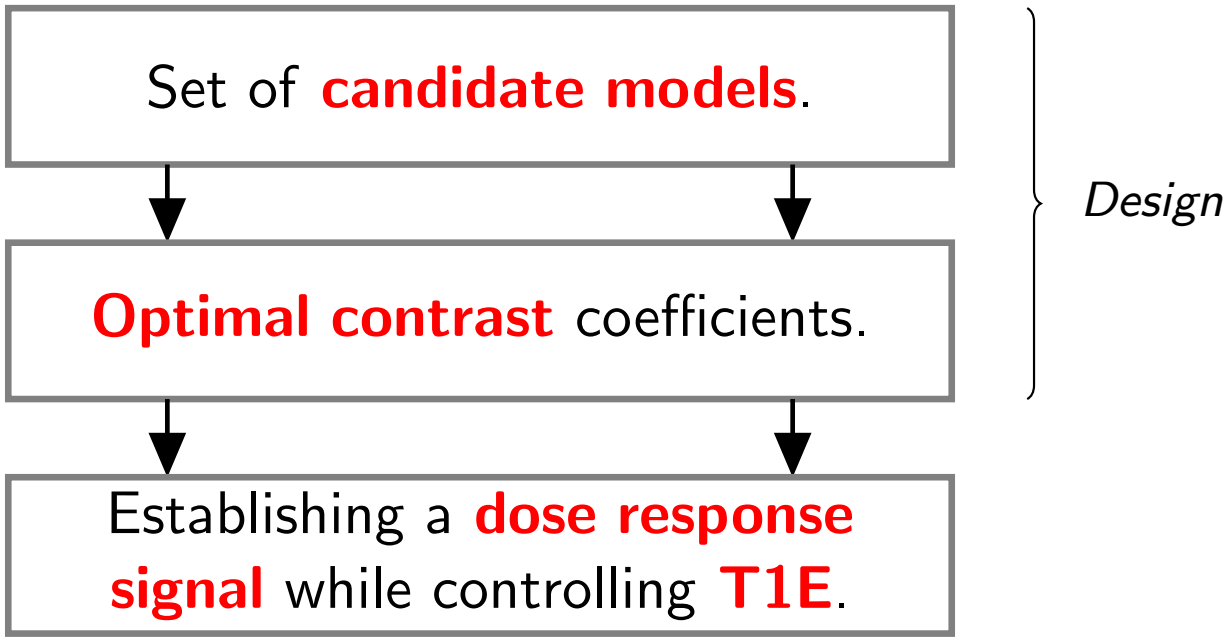

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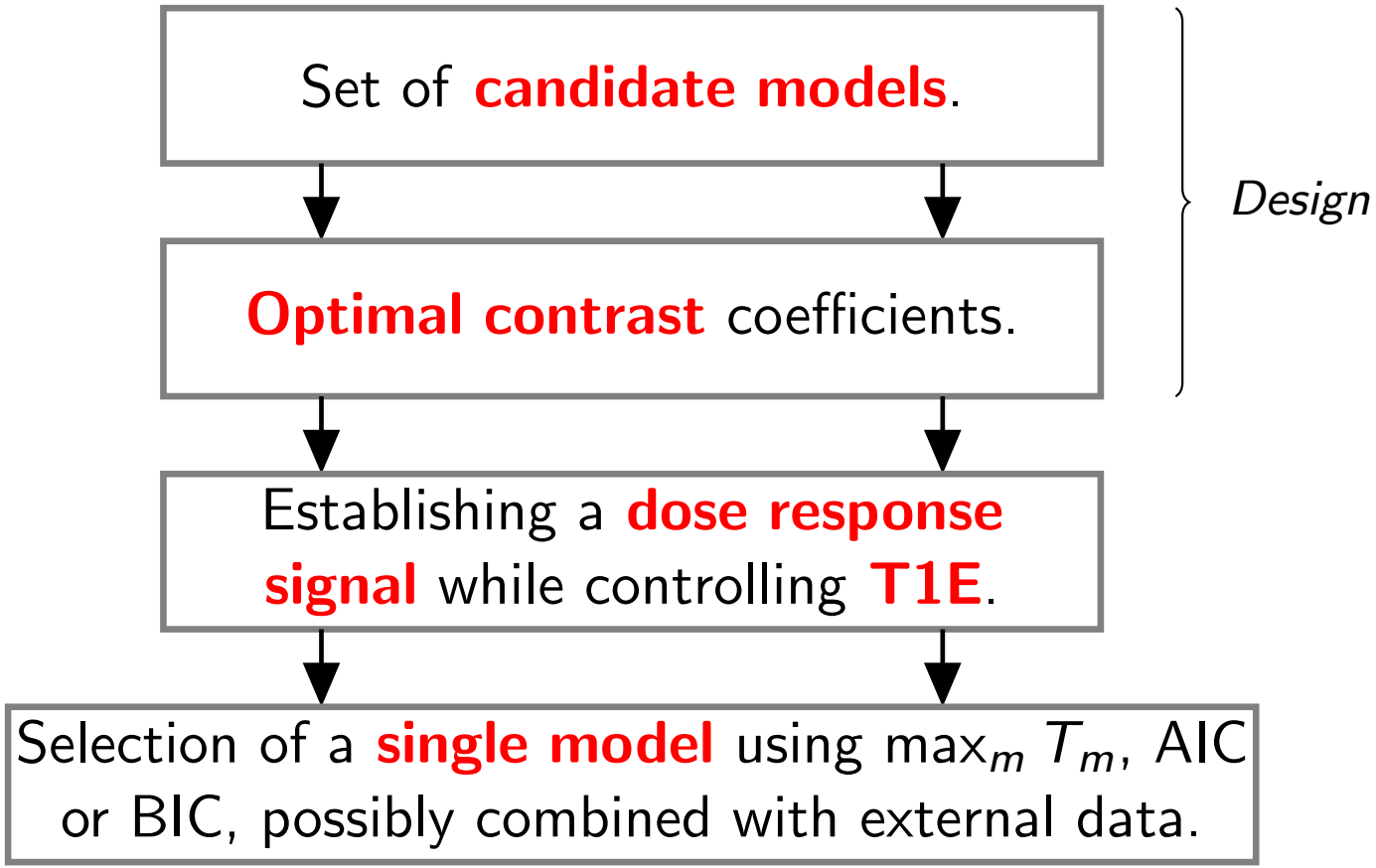
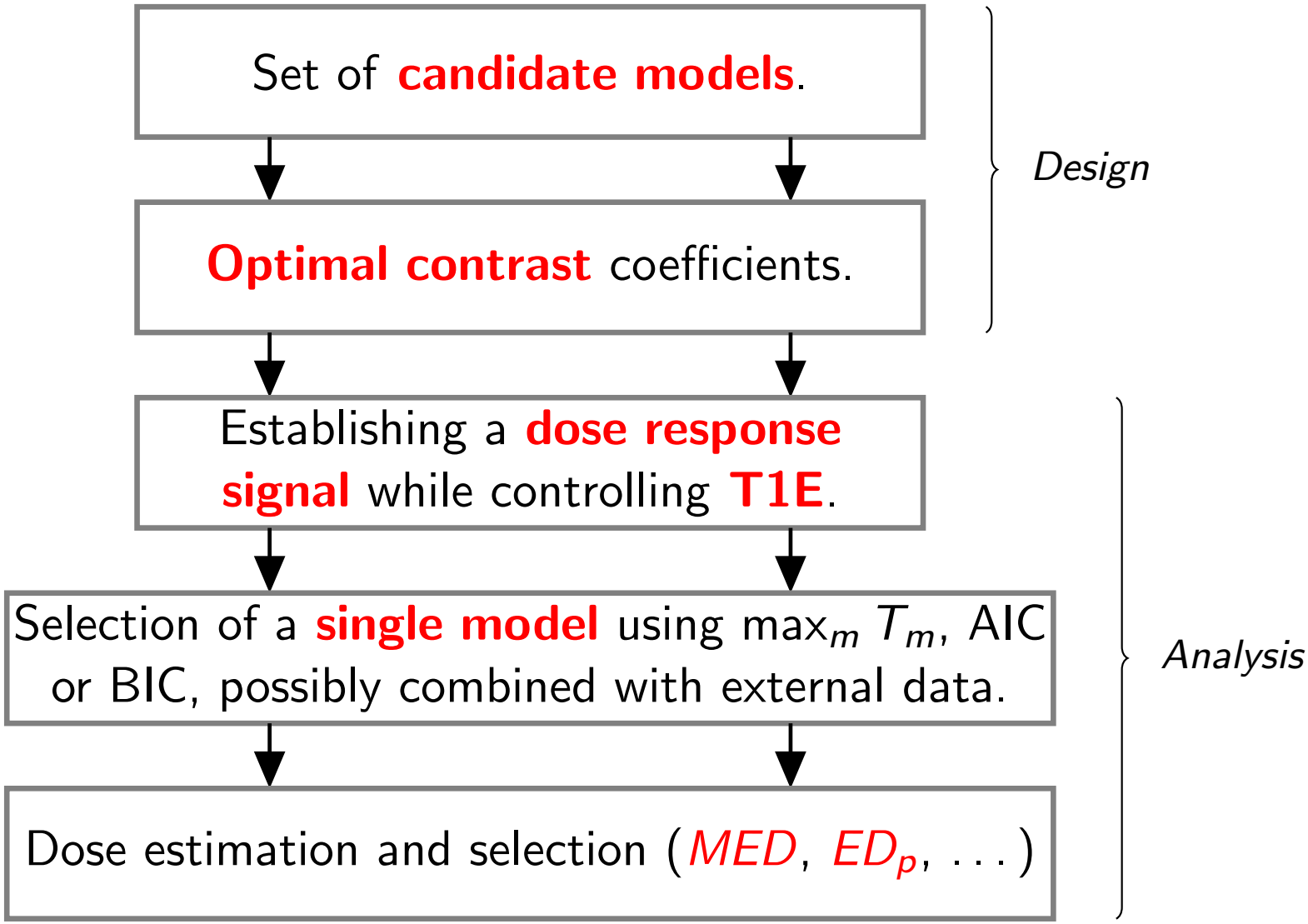
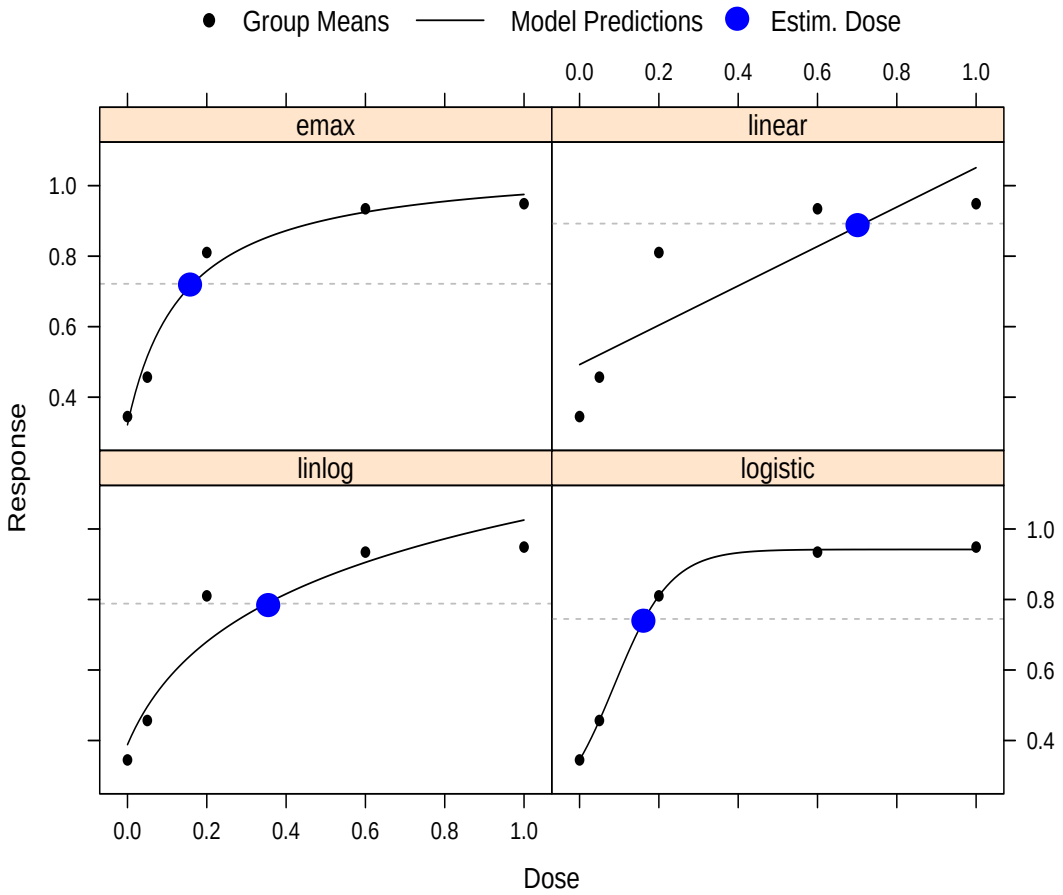


Hybrid aprroach - MCP-Mod (Bretz et al. [2005])



Hybrid aprroach - MCP-Mod (Bretz et al. [2005])

- For $\Delta = 0.4$



- $MED_{emax} = 0.1642.$
- $MED_{linear} = 0.7161.$
- $MED_{linlog} = 0.3655.$
- $MED_{logistic} = 0.1636.$

Hybrid aprroach - MCP-Mod (Bretz et al. [2005])

- **MCP-Mod**
  - **Provides the flexibility** of modeling for dose estimation.
  - **Robustness to model** misspecification.

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Future work

- Combining **Bayesian Model Averaging** (BMA) and **MCPMod**
  - Focus only on **statistically significant models** to use in BMA approach, starting with **advanced weight estimates**.
  - **Define** a rule for the choice of the **reference model**.
  - **Evaluate** difference between single **model approach**, **MCPMod + BMA**, and **full BMA**.
  - Start with **non-adaptive** case.
  - Move to an **adaptive** case.
- **Adaptive** clinical trial designs with multiple doses and use of **modeling approaches**:
  - to **establish** a positive dose-response **profile**.
  - to **increase the power** of declaring effective dose statistically significant.
  - to support **dose selection** at an adaptive interim analysis.
  - to use **closure principle** for the control of **T1E** rate in a strong sense.

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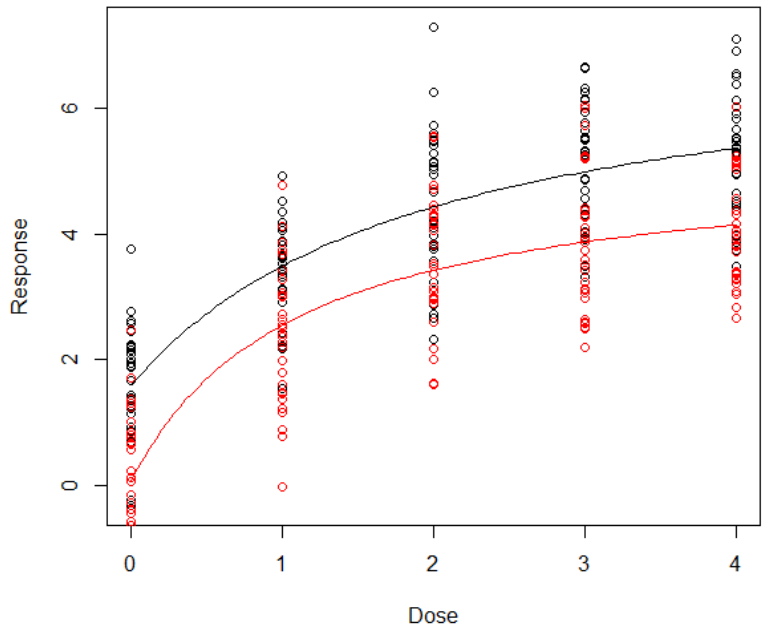
THANK YOU

IDEAL Project

WP3-Extrapolating dose response information to small populations

Task 3.1: New statistical measures for similarity of dose-response between a source and a target population



IDEAL Project

Introduction

- In clinical trials the observation of different populations and their reaction on medicinal drugs is of huge importance
- Our work package deals with extrapolation of dose response information from a given source population to a target population which is much smaller in size
- In this regard regression models are very important
- In our first task we focused on measuring the similarity of two dose response curves
- Main objective of the last half year: improvement of the accuracy and the computational effort of confidence bands
- Furthermore development of a statistical test measuring the similarity of two dose response curves

IDEAL Project

New Confidence Bands

- We consider two models

$$Y_{1,i} = m_1(x_i, \alpha) + \epsilon_{1,i} \; ; \; i = 1, ...n_1$$

$$Y_{2,i} = m_2(x_i, \beta) + \epsilon_{2,i} \; ; \; i = 1, ...n_2$$

  on the same covariate region D

- We define two stochastic processes:

$$p_n(x) = m_1(x, \widehat{\alpha}) - m_2(x, \widehat{\beta}) - (m_1(x, \alpha) - m_2(x, \beta))$$

$$G(x) = \nabla m_1(x, \alpha)^T \cdot \sigma_1 \cdot \sqrt{\lambda} \cdot \Sigma_1^{1/2} \cdot Z_1 - \nabla m_2(x, \beta)^T \cdot \sigma_2 \cdot \sqrt{\frac{1}{1 - \frac{1}{\lambda}}} \cdot \Sigma_2^{1/2} \cdot Z_2$$

- $\{G(x)\}_{x \in D}$ is a centered Gaussian process
-

$$\left\{\sqrt{n_1 + n_2} \cdot p_n(x)\right\}_{x \in D} \xrightarrow{\mathcal{D}} \{G(x)\}_{x \in D}$$

IDEAL Project

With $\mu := q_{1-\alpha}(\max_{x \in D} |\widehat{G(x)}|)$ it holds

$$\lim_{\substack{n_1, n_2 \to \infty \\ \frac{n_1+n_2}{n_1} \to \lambda}} \mathbb{P}(L(x) \leq m_1(x, \alpha) - m_2(x, \beta) \leq U(x) \ \forall \ x \in D) = 1 - \alpha$$

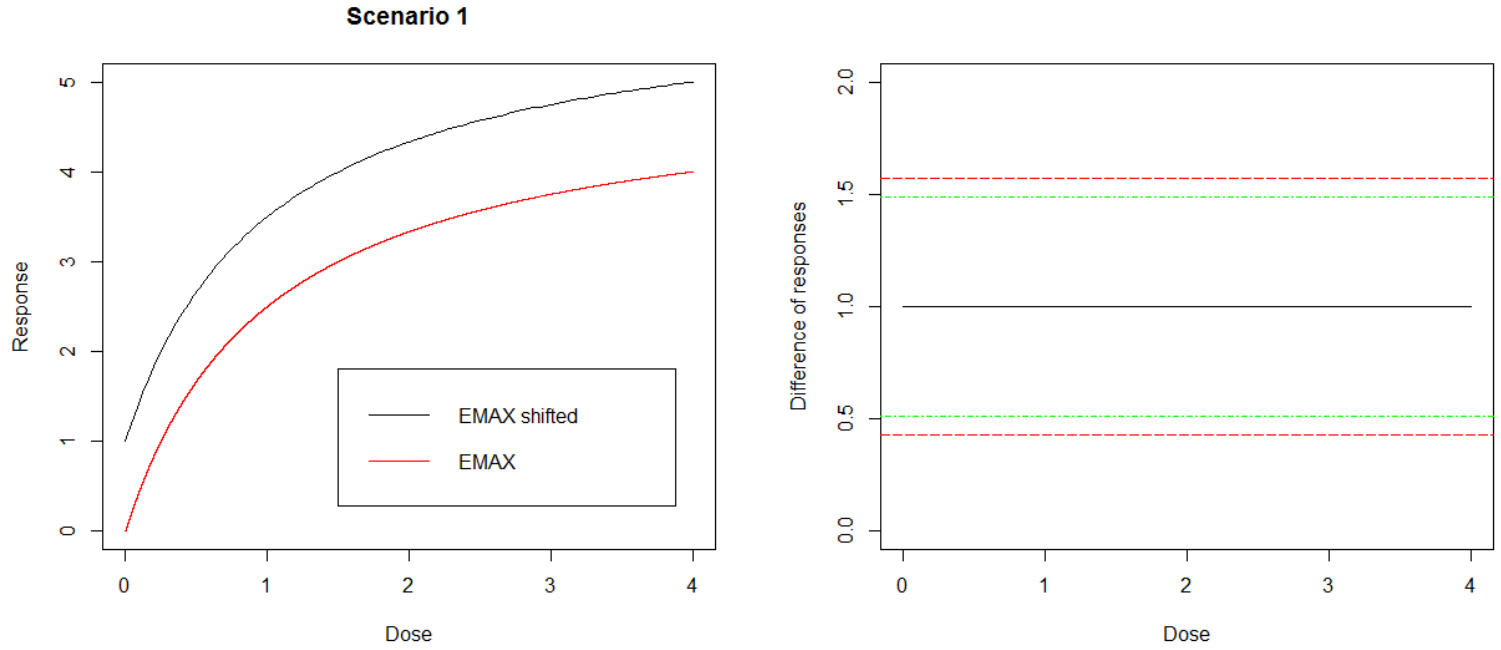


Figure: Two EMAX models with constant difference $\delta = 1$. The right figure shows the mean difference curve and the confidence bands.

IDEAL Project

- New statistical tests using the maximum absolute deviation and the absolute difference of the MEDs as different test statistics $\rightarrow$ much higher power)
- next working period:
  $\rightarrow$ accomplish the R software
  $\rightarrow$ compare our results to the currently available techniques
  $\rightarrow$ proceed with the second task- the extrapolation of efficacy and safety information

Randomisation for the design of clincal trials

Diane Uschner

Uniklinik RWTH Aachen

June 28, 2014

FP7 HEALTH 2013 - 602552

Objectives of Randomisation (ICH E9)

- Statistical basis for quantitative evaluation of the evidence relating to treatment effects.
- Produce treatment groups with similar distribution of prognostic factors.
- In combination with blinding: Help avoid bias in the selection and allocation of subjects arising from predictability of treatment assignments (selection bias).

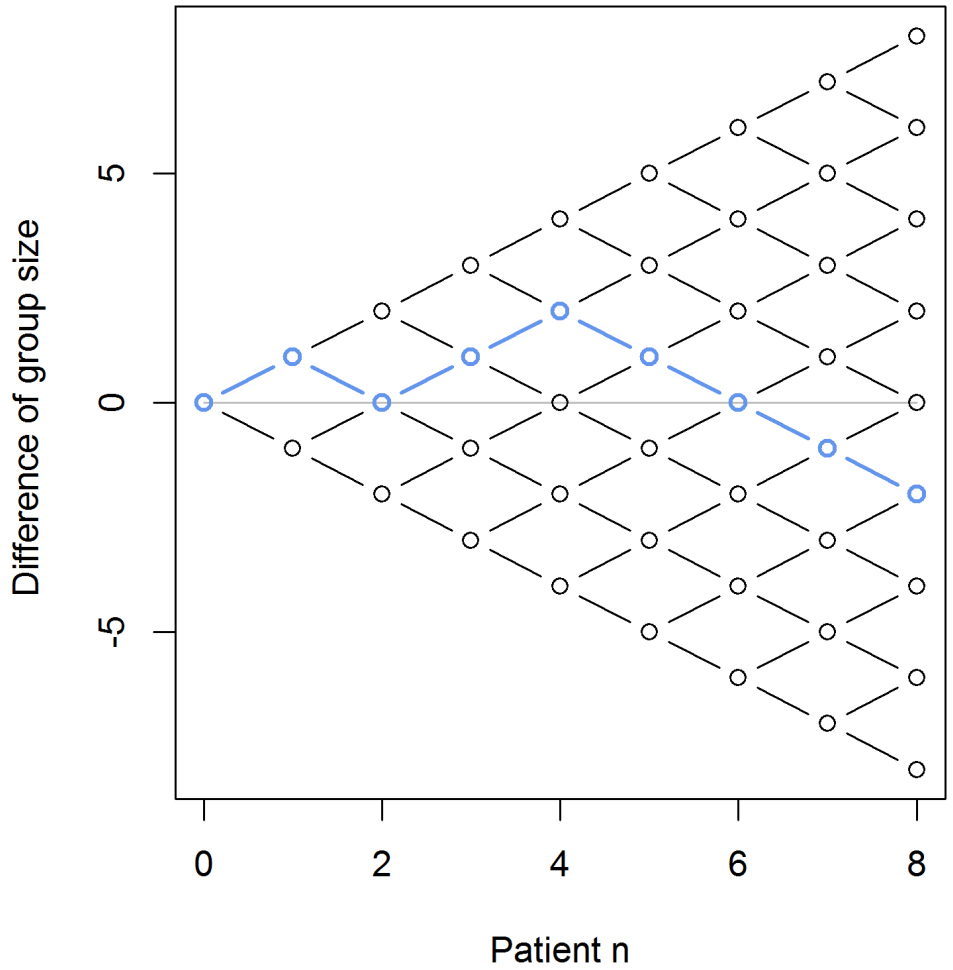
Randomisation Procedure

In a two-armed trial, a randomisation procedure M is a probability distribution over the set $\Gamma = \{-1, 1\}^N$

Idea

Use suitable randomisation procedure to reduce the effect of all kinds of bias.

Set of all sequences



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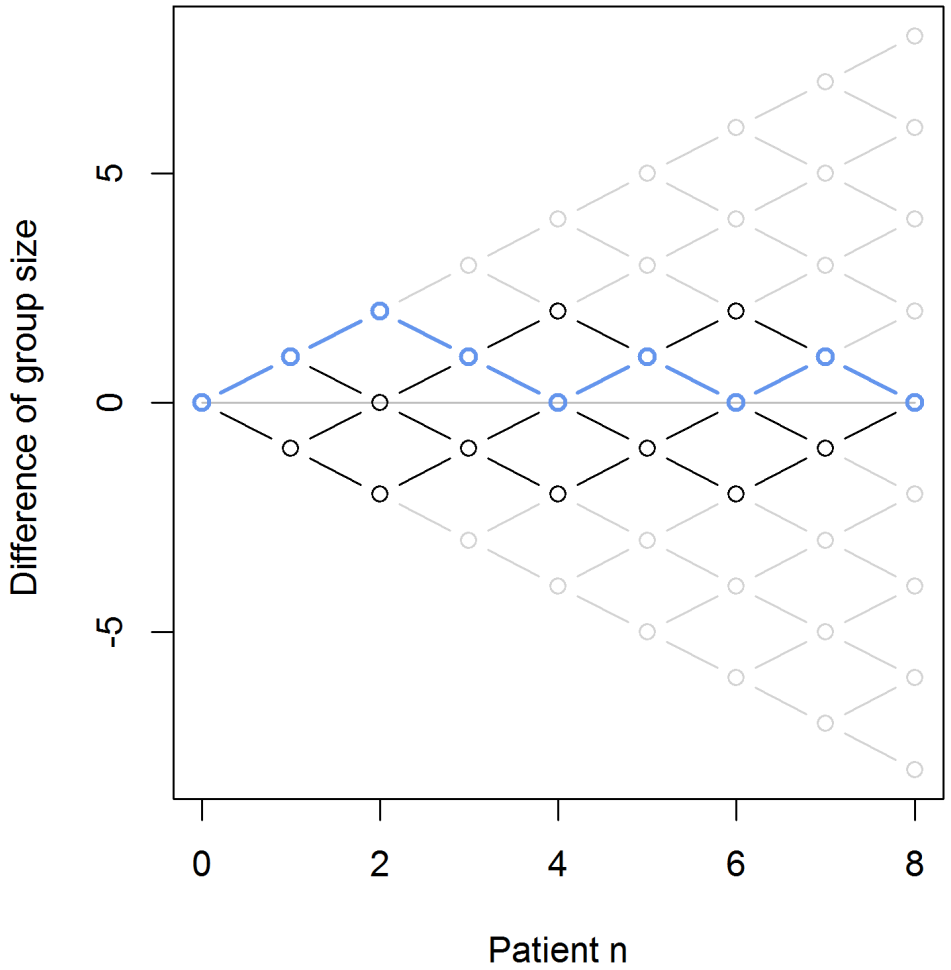
MP's set of sequences



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Tasks in work package 2

D1 Bias assessment for randomisation procedures.

D2 Development of adequate randomisation procedures in small population groups.

D3 Development of a randomisation test in small population groups.

Correct Guesses - One Method assessing the Impact of Selection Bias in Clinical Trials

David Schindler

Department for Medical Statistics
RWTH Aachen

June 30, 2014

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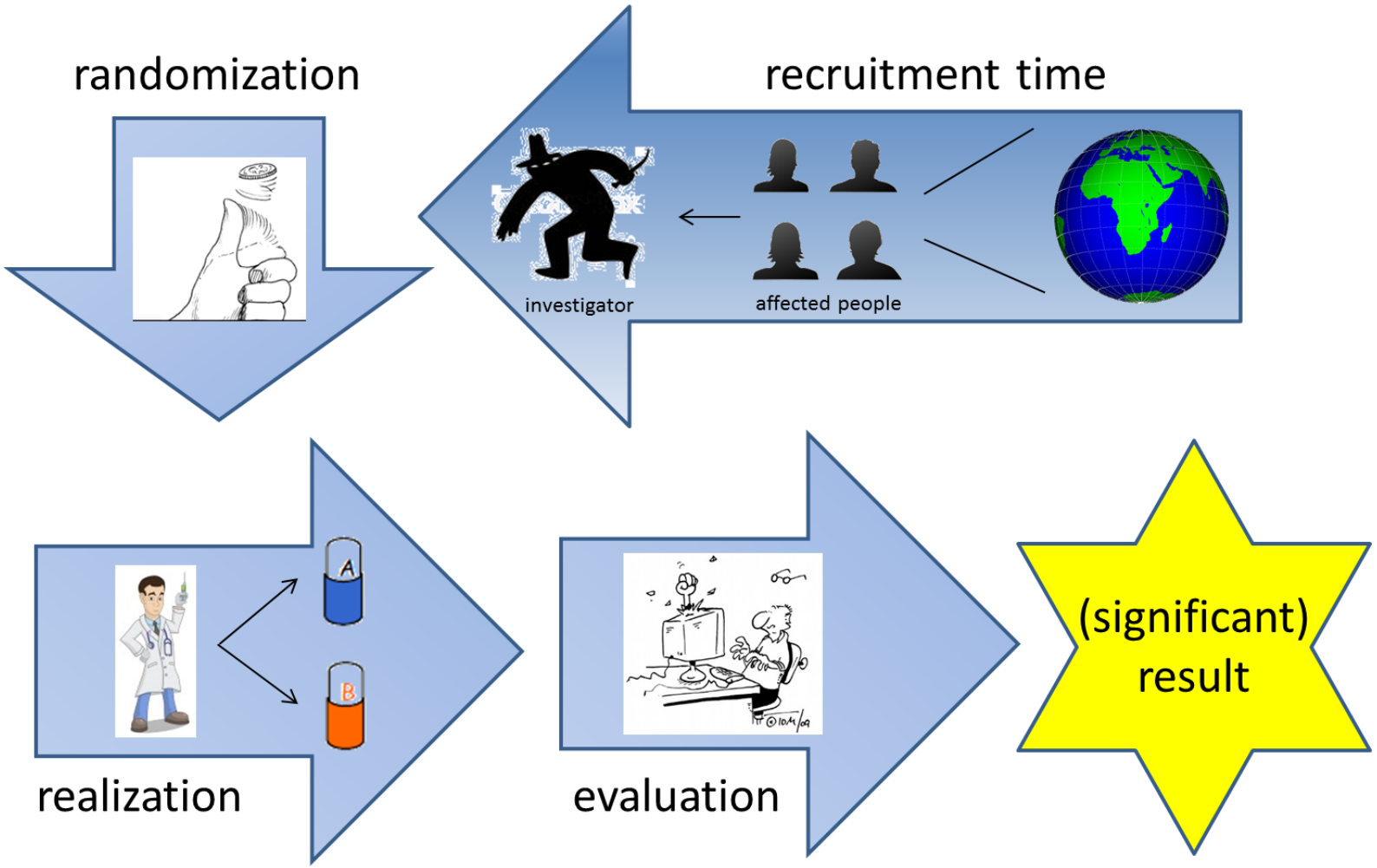
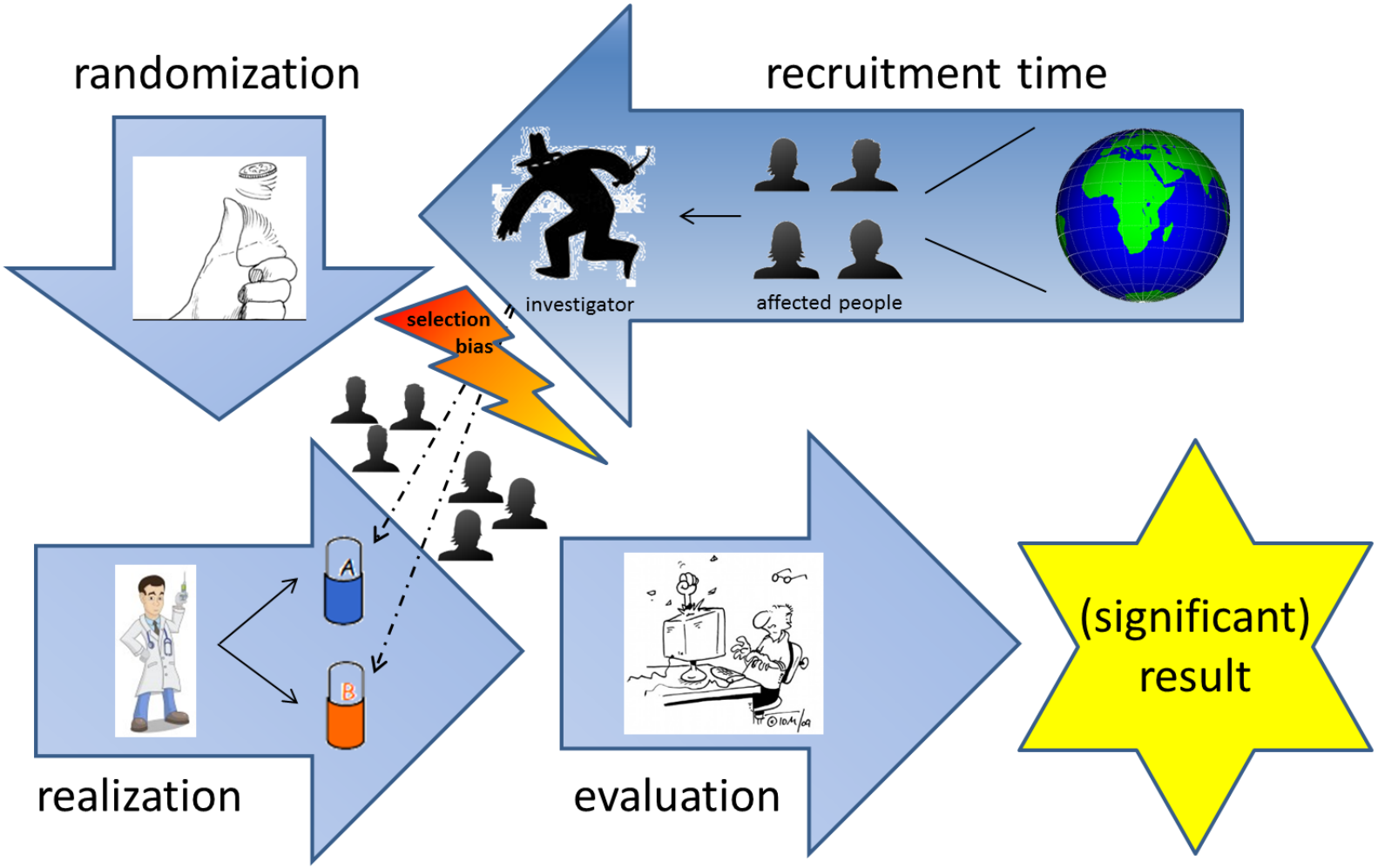
Doubly blinded study



Doubly blinded study



Correct Guesses (CG)

- Let $\boldsymbol{T} = (T_1, \ldots, T_n)$ and $T_i \in \{0, 1\}$ be a randomization sequence. We write:

$$T_i = \begin{cases} 1 & \text{patient } i \text{ is assigned to A} \\ 0 & \text{patient } i \text{ is assigned to B} \end{cases}.$$

- Under the assumption of final balance in the trial, it is opportune for the investigator to guess

$$g(T_i) := \begin{cases} 0 & N_A(i-1) > N_B(i-1) \\ Ber(0.5) & N_A(i-1) = N_B(i-1) \\ 1 & N_A(i-1) < N_B(i-1) \end{cases}$$

Measureing the CG and research tasks

- We define the expected number of CG under the use of a randomization method M:

$$CG_M := E_M(E(\#\{i = 1, \ldots, n | g(T_i) = T_i\}).$$

- Research tasks:
  - Compare the CG for several randomization methods and their settings.
  - Which randomization methods have low CG and are meaningful for clinical trials with small population groups?
  - Investigate covariance structure of T_i and T_j with $i \neq j$ in dependence of the randomization method.

Chronological bias in randomized clinical trials

Miriam Tamm

Department of Medical Statistics
RWTH Aachen

June 30, 2014

FP7 HEALTH 2013 - 602552

Time trends & Chronological bias

- Sequential recruitment of patients
- Time trends during the recruitment phase

$\Rightarrow$ Risk of bias in the results of the clinical trial (**Chronological bias**)

Randomization: Balance between treatment groups throughout the recruitment time

In context of rare diseases

„A common problem with trials in rare diseases is that recruitment is slow because patients are so rare [...].“ (EMA, Guideline on clinical trials in small populations, 2006)

- Rare Diseases $\Rightarrow$ Long recruitment time
- Changes over the course of recruitment

$\Rightarrow$ Increased susceptibility to chronological bias

Model

Parallel group design: Two treatments A and B with equal sample sizes, randomization sequence $\mathbf{Z} = (Z_1, \ldots, Z_n)$ with realization $\mathbf{z} = (z_1, \ldots, z_n) \in \{0,1\}^n$

Model

$$Y_i = \mu_A Z_i + \mu_B (1 - Z_i) + \tau(i) + \sigma e_i$$

with time trend $\tau(i) \in \mathbb{R}$ and with $e_i \sim N(0,1)$ independent of Z_i, $i = 1, \ldots, n$, $n \in 2\mathbb{N}$.

- Linear trend: $\tau(i) = \lambda \cdot (i-1)$
- Step: $\tau(i) = \lambda \cdot \mathbb{1}_{\{i \geq c\}}$ $\quad (i = 1, \ldots, n,\ \lambda \in \mathbb{R},\ c \geq 1)$
- Logarithmic trend: $\tau(i) = \lambda \cdot \log(i)$

Example ($n = 6$, Linear trend)

RAR: $\binom{6}{3} = 20$ possible sequences

	Z:		Bias:
AAABBB			-3λ
AABABB			$-7/3\lambda$
AABBAB	ABAABB		$-5/3\lambda$
AABBBA	ABABAB	BAAABB	$-\lambda$
ABABBA	ABBAAB	BAABAB	$-1/3\lambda$
BABAAB	BAABBA	ABBABA	$1/3\lambda$
BBAAAB	BABABA	ABBBAA	λ
BBAABA	BABBAA		$5/3\lambda$
BBABAA			$7/3\lambda$
BBBAAA			3λ

Example ($n = 6$, Linear trend)

MP with maximum tolerated imbalance (MTI) of 2: 18 possible sequences

	Z:		Bias:
AAABBB			-3λ
AABABB			$-7/3\lambda$
AABBAB	ABAABB		$-5/3\lambda$
AABBBA	ABABAB	BAAABB	$-\lambda$
ABABBA	ABBAAB	BAABAB	$-1/3\lambda$
BABAAB	BAABBA	ABBABA	$1/3\lambda$
BBAAAB	BABABA	ABBBAA	λ
BBAABA	BABBAA		$5/3\lambda$
BBABAA			$7/3\lambda$
BBBAAA			3λ

Example ($n = 6$, Linear trend)

MP with maximum tolerated imbalance (MTI) of 1: 8 possible sequences

Z:			Bias:
AAABBB			-3λ
AABABB			$-7/3\lambda$
AABBAB	ABAABB		$-5/3\lambda$
AABBBA	ABABAB	BAAABB	$-\lambda$
ABABBA	ABBAAB	BAABAB	$-1/3\lambda$
BABAAB	BAABBA	ABBABA	$1/3\lambda$
BBAAAB	BABABA	ABBBAA	λ
BBAABA	BABBAA		$5/3\lambda$
BBABAA			$7/3\lambda$
BBBAAA			3λ

FP7 HEALTH 2013 - 602552

Research tasks

- Comparing different randomization procedures regarding
  - Bias and variance of estimate of treatment effect
  - Impact on results of statistical inference (type I error, power)
- Overall properties
- Maximum extent of bias in worst-case scenarios

Statistical issues in the design of small population trials

Artur Araujo

Objective:

Determine the effect of medical treatments. Does the treatment really improve a patient's health and quality of life?

How?

Measure some outcome or explained variable that reflects a patient's state of health, both under the presence and absence of treatment. If all variables that influence the outcome variable are kept equal under presence and absence of treatment, then the difference in outcome is due to the effect of treatment. This procedure is called experiment or clinical trial.

Issues:

Outcome or explained variables are mathematical functions of one or many explanatory variables. Several of such mathematical relationships are known to science and find many applications in engineering. Due to the complexity of the universe and limitations of the human mind its difficult to account for all explanatory variables in mathematical models. In practice unknown or unaccounted for explanatory variables change across measurements of outcome and variability is observed! The true difference due to treatment can become very difficult to determine! Is the observed difference in outcome due to treatment or due to unknown explanatory variables?

Parallel

A sample of subjects is divided in as many groups as distinct treatments being compared. Each group receives only one treatment. So each subject receives only one treatment.

Crossover

Subjects are given sequences of treatments with the objective of studying differences between individual treatments (or sub-sequences of treatments).

N-of-1

A single subject receives several sequences of treatments.

Small population issues

1. Sample size calculations in clinical trial designs are based on power, the probability to detect a difference when a difference in fact exists.
2. The power increases as the variance of the difference in means decreases.
3. In general the variance decreases as sample size increases.

How can sample size be optimized to deliver usefull information given the resources available?

Optimizing the trial

a. Increase the signal (difference in means).
b. Reduce the noise (variance of difference in means).
    i. Increase the number of subjects.
    ii. Reduce the variance of measurements.
    iii. Put more variables in models.
    iv. Opt for more efficient designs, for example cross-over trials.
    v. Increase the number of measurements, by adding more periods or measure more frequently within periods.
    vi. Use adequate statistical modelling.
    vii. Choose more sensitive outcome measures (surrogate endpoints).
    viii. Use correct transformation of variables.
    ix. Reduce variability in treatment delivery.
c. Reduce “decision precision” by accepting higher type I and or type II error rates.

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8. Sheather, S., *A Modern Approach to Regression with R*. 2009: Springer.
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10. Julious, S.A., *Sample Sizes for Clinical Trials*. 2010: Taylor & Francis.
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Thanks for your attention!

CONVEX OPTIMIZATION METHODS IN GENOME-WIDE ASSOCIATION STUDY (GWAS)

Damian Brzyski

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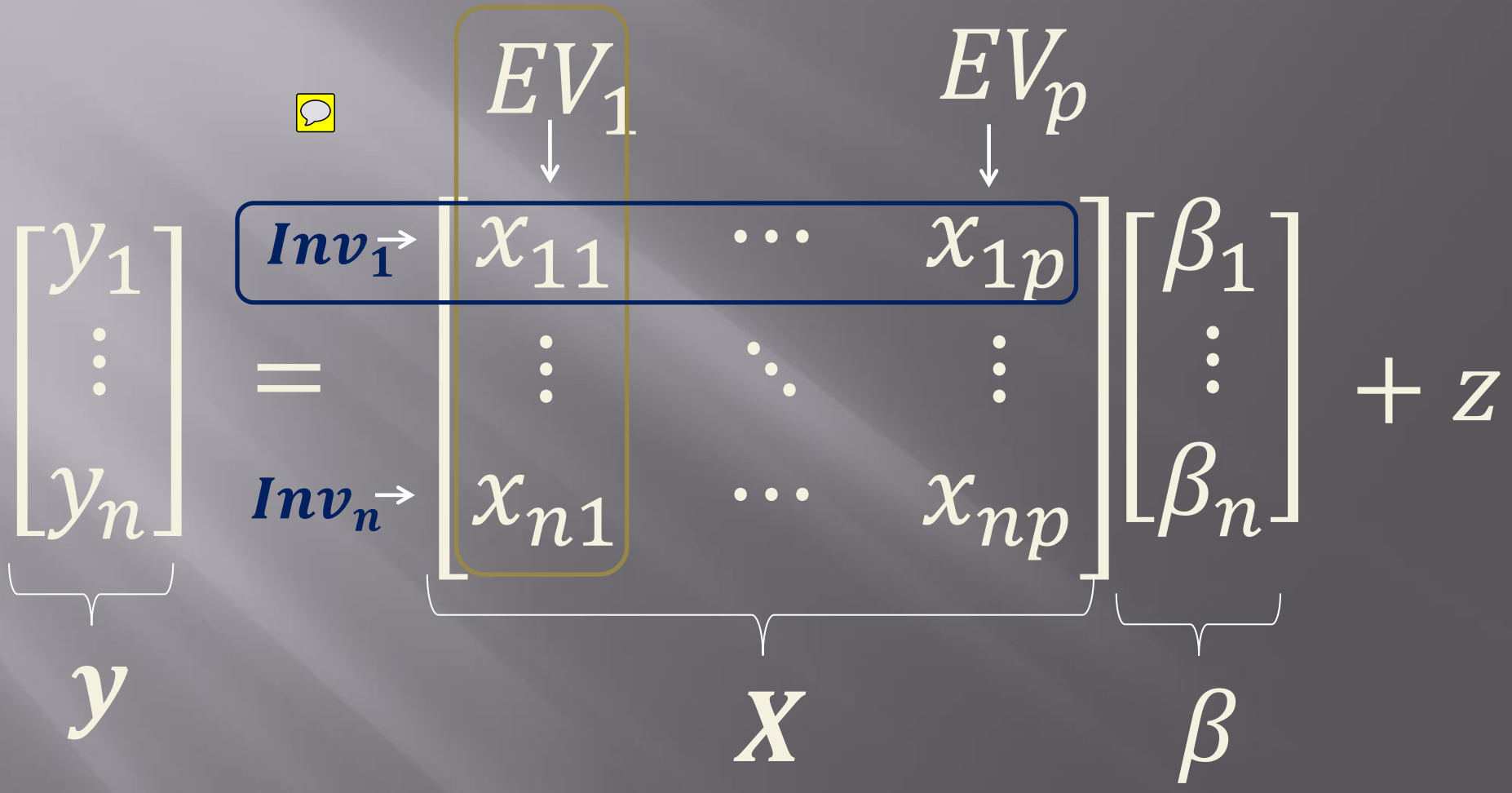
Considered model



$x_{jk} \in \{-1, 0, 1\}, \; z \sim N(0, \sigma I_n)$

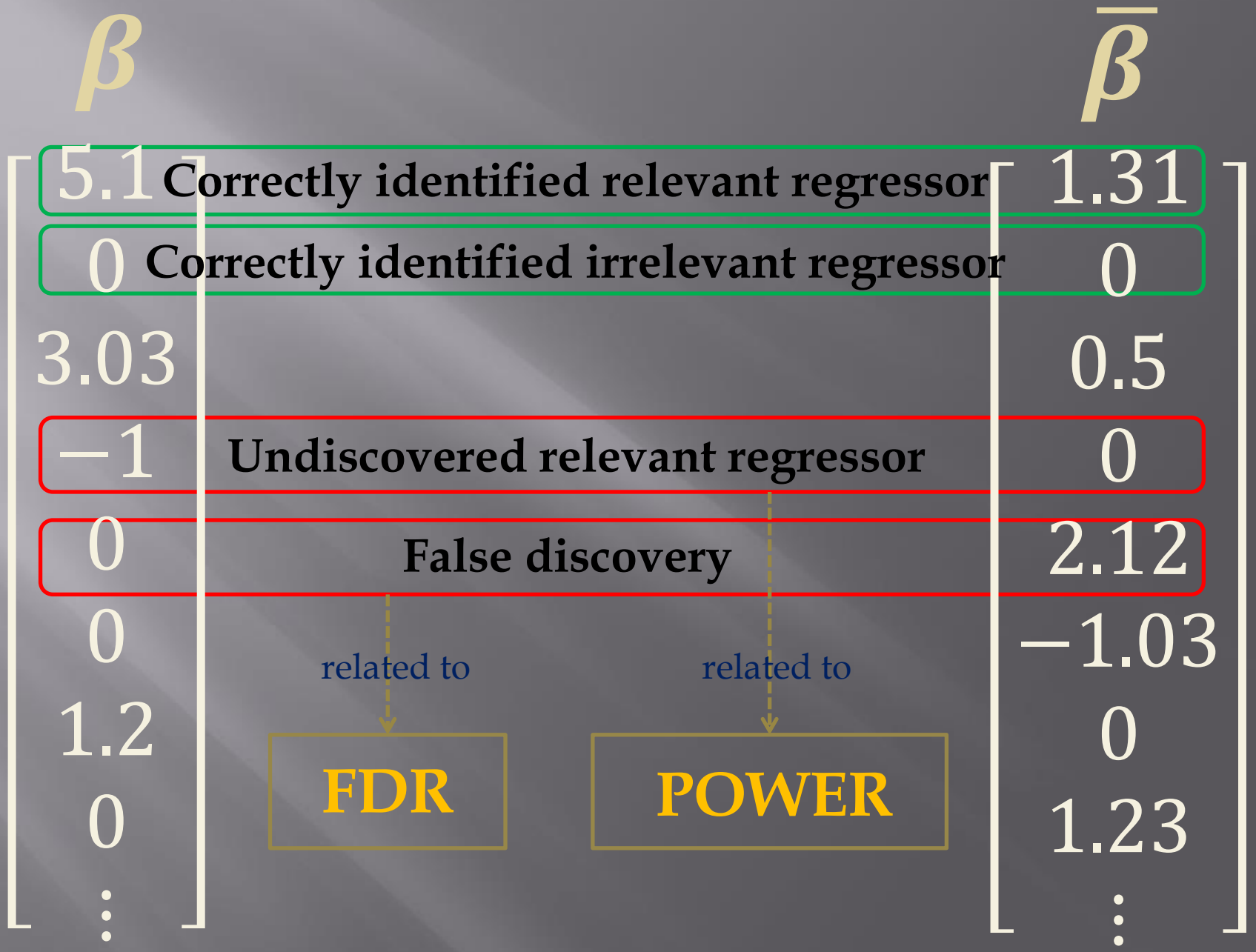
Applied method: SLOPE

[1] Bogdan, M., van den Berg, E., Su, W., Candès E. J., Statistical Estimation and Testing via the Ordered l_1 Norm, 2013.

For some $\lambda_1 \geq \cdots \geq \lambda_p \geq 0$ SLOPE is defined as solution to

$$\underset{b}{argmin} \left\{ \frac{1}{2} \|y - Xb\|_{l_2}^2 + \sigma \sum_{i=1}^{p} \lambda_i \cdot |b|_{(i)} \right\}$$

where $|b|_{(i)}$ denotes ith largest absolute value of coefficients of b


β
$\bar{\beta}$
5.1
0
3.03
−1
0
0
1.2
0
⋮
1.31
0
0.5
0
2.12
−1.03
0
1.23
⋮
Correctly identified relevant regressor
Correctly identified irrelevant regressor
Undiscovered relevant regressor
False discovery
related to
related to
FDR
POWER

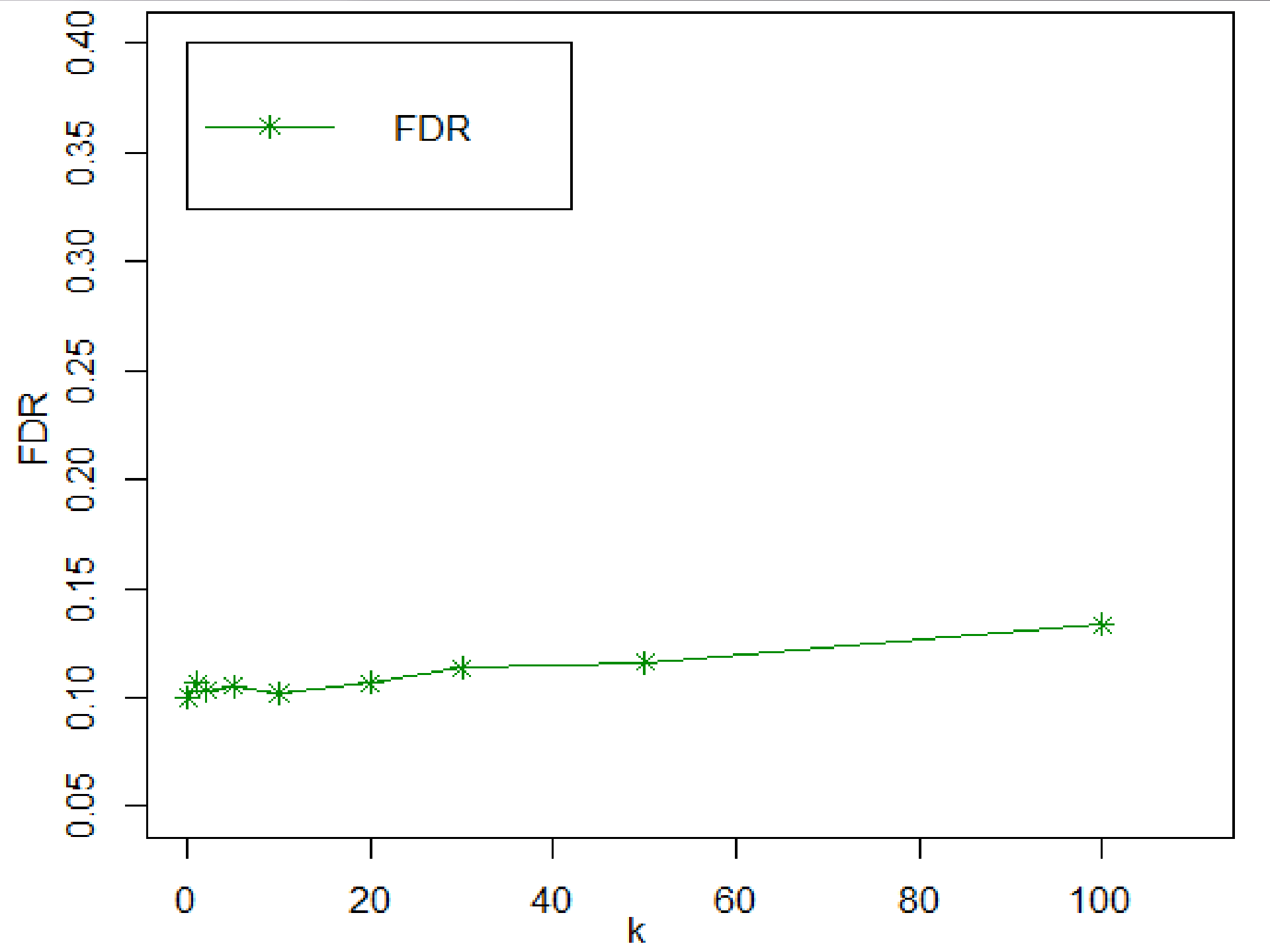
Results

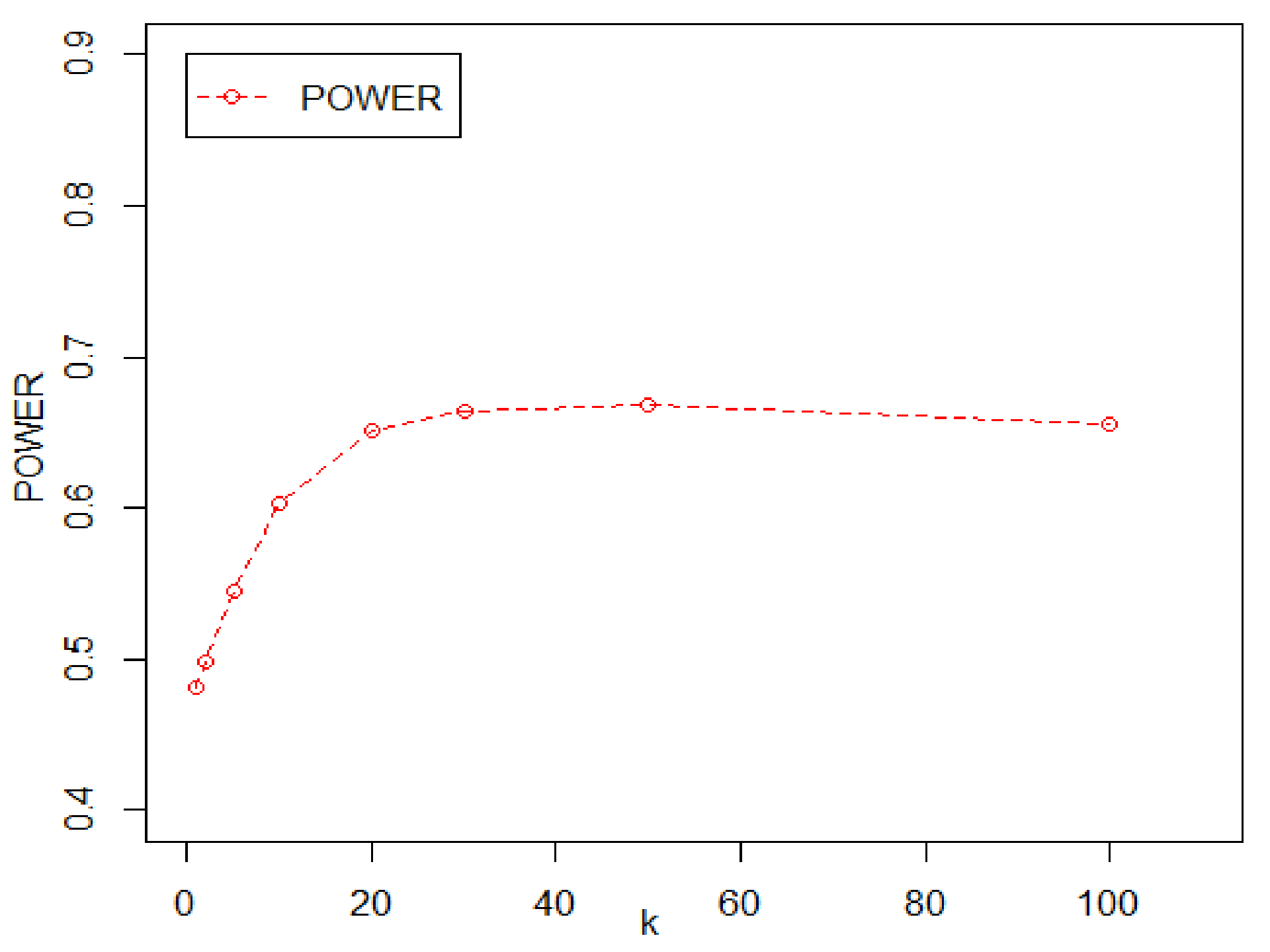
$\boldsymbol{X}$- data matrix with p=26315 columns and n=5402 rows

$\boldsymbol{\beta}$- constant on k randomly selected places, zeros in other locations

$\boldsymbol{y}$- generated as $\mathbf{X}\boldsymbol{\beta} + \boldsymbol{z}$, where $z \sim N(0, I_n)$

Target level of FDR equal to 0.1


FDR
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
FDR
0
20
40
60
80
100
k


POWER
0.9
0.8
0.7
0.6
0.5
0.4
POWER
0
20
40
60
80
100
k

THANK YOU FOR YOUR ATTENTION

damian.brzyski@uj.edu.pl

Subspace clustering

Piotr Sobczyk

Politechnika Wrocławska

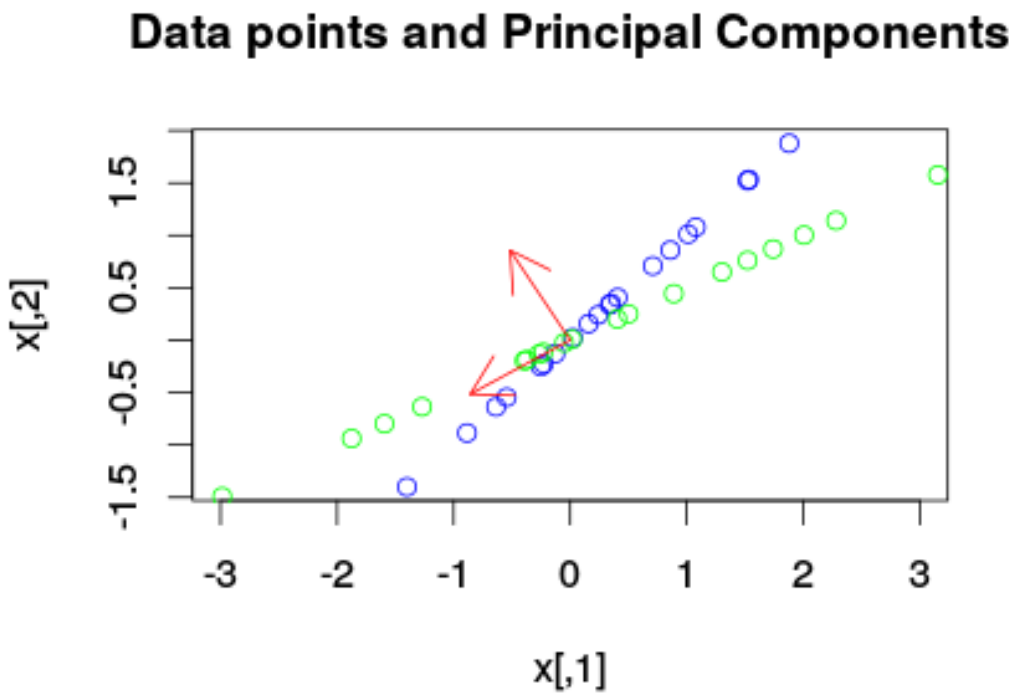
June 30, 2014

Outline

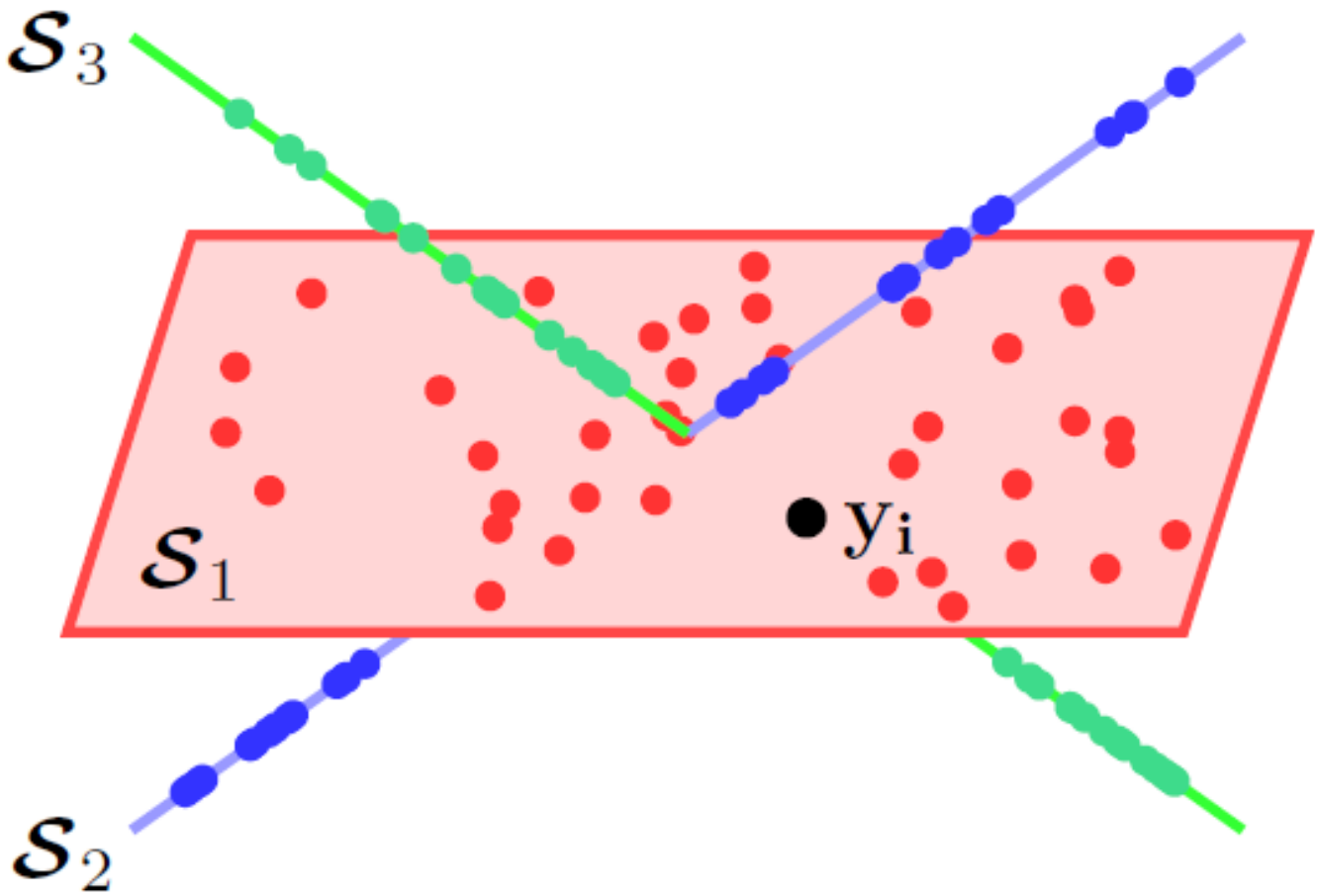
- Motivation - PCA
- Subspace clustering
- Application to biology

PCA

Getting meaningful model requires dimensionality reduction



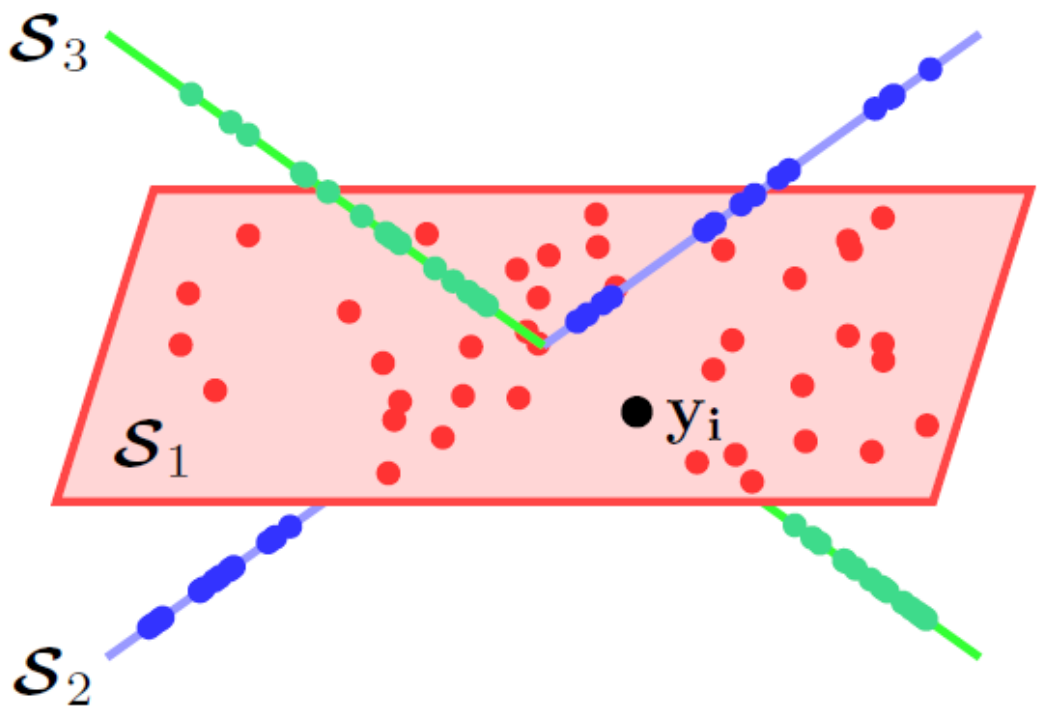
Subspace clustering



Subspace clustering

We need to find

- # subspaces
- Dimension of each subspaces
- Point segmentation



Clustering around latent variables - K-means based method

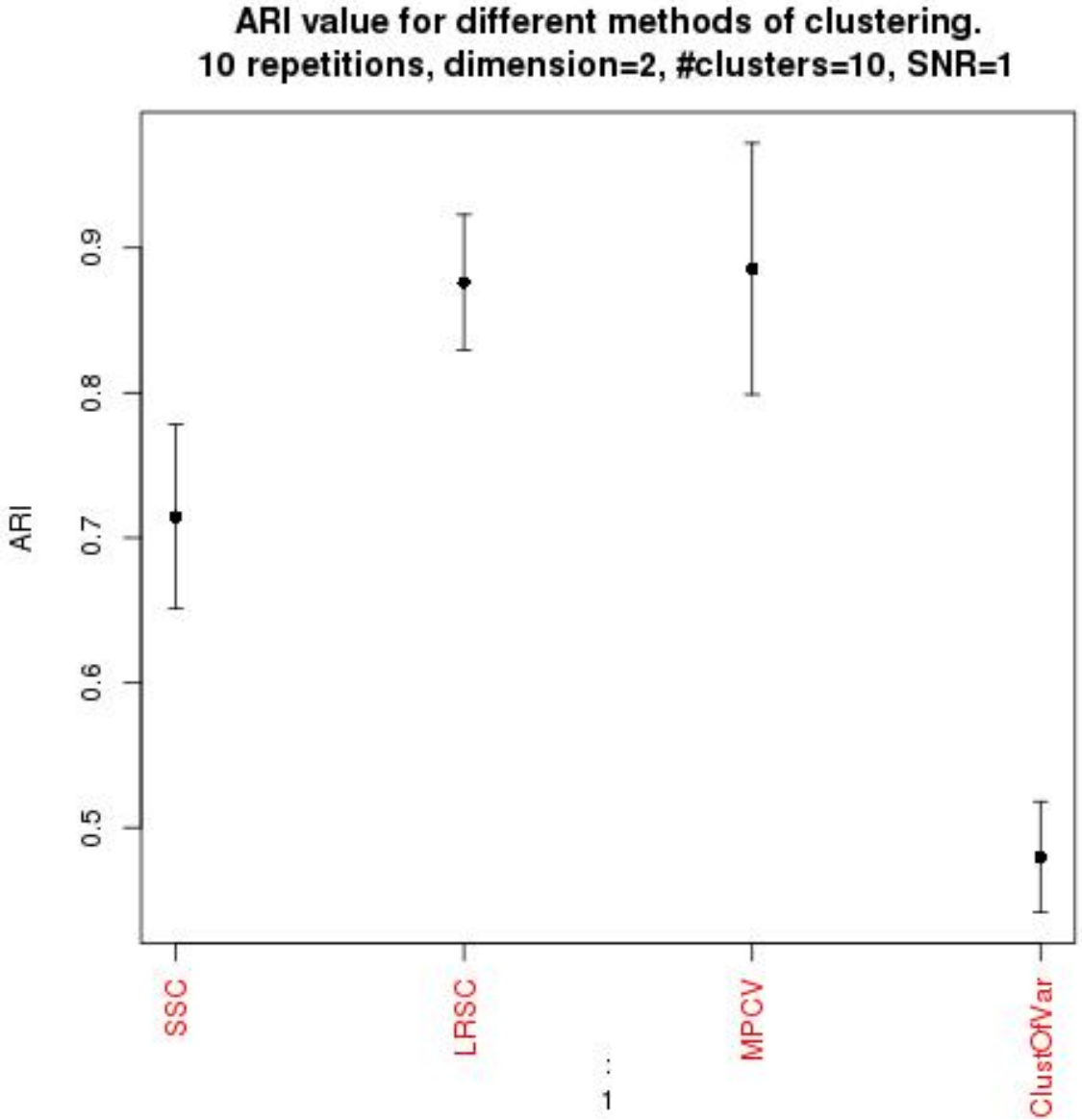
Until convergance is obtained:

1. Reassign variables to the closest center (most correlated subspace)
2. Compute new centers (principal components)

Number of subspaces choosen with information criterion

Application to genomics

- Different clusters are gene pathways
- For each pathway we extract only a number of important factors
- Still missing: introducing aprior knowledge


ARI value for different methods of clustering.
10 repetitions, dimension=2, #clusters=10, SNR=1
ARI
0.5
0.6
0.7
0.8
0.9
SSC
LRSC
MPCV
ClustOfVar
1

Estimating number of clusters using BIC

	0.5	1	2	4	8	16
dim=2	5.0 ± 0	10.3 ± 0.6	11.3 ± 0.9	11.7 ± 1.2	10.6 ± 0.8	10.1 ± 0.3
dim=3	5.0 ± 0	5.5 ± 0.9	11.0 ± 1.1	11.9 ± 1.8	10.7 ± 0.6	10.2 ± 0.4

Table : Average number of choosen subspaces (true number is 10) for different signal to noise scenarios and subspace dimensions. Number of variables is 200. Number of observations is 100. 100 repetitions

Definition (Missclassification rate)

Let us assume that there are two segmentation of n points - X and Y.

They are both divided into K clusters. $X = (X_1, ..., X_K)$, $Y = (Y_1, ..., Y_K)$

We find a best match among all permutations π if clusters numbers with

respect to measure

$$\text{Missclassification} = 1 - \max_{\pi} \frac{\#\text{ points } p \text{ correctly classified}}{\#\text{ points}} =$$

$$= 1 - \max_{\pi} \frac{\sum_p \sum_i^K \mathbf{1}_{p \in X_i \text{ and } p \in Y_{\pi(i)}}}{\#\text{ points}}$$

Definition (Rand Index)

Let us assume that there are two segmentation of n points - X and Y. X is divided into r subsets and Y is divided into s subsets. Rand index is

$$\mathbf{R} = \frac{a+b}{\binom{n}{2}}$$

where $a =$

pairs of points that are in the same set in X and in the same set in Y

$b =$

pairs of points that are in different set in X and in different set in Y

Adjusted Rand Index (ARI)

Including the expected number of correct seperations.

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- Rene Vidal, *Subspace clustering* IEEE Signal Processing Magazine, 2011
- Vidal and Elhamifar *JSparse Subspace Clustering* 2009
- Marie Chavent, Benoit Liquet, Vanessa Kuentz-Simonet, Jerome Saracco, *ClustOfVar: An R Package for the Clustering of Variables*, Journal of Statistical Software, 2012
- Pankaj K. Agarwal, Nabil H. Mustafa *k-Means Projective Clustering*, Proceeding PODS '04 Proceedings of the twenty-third ACM SIGMOD-SIGACT-SIGART symposium on Principles of database systems,

ADAPTIVE DOSE-FINDING DESIGNS IN ONCOLOGY FOR COMBINATION OF MOLECULES AND MOLECULARLY TARGETED AGENTS

Marie-Karelle Riviere

INSERM UMR 1138, Centre de Recherche des Cordeliers, Team 22: Information Sciences to support Personalized Medicine

Phase I

- First stage of human experimentation with a new drug or combination
- Objective: to find a dose level associated with "acceptable" toxicity
- In Anti-cancer cytotoxic agents
  - Acceptable toxicity can be high
  - Toxicity and efficacy increase with dose

Experimental design

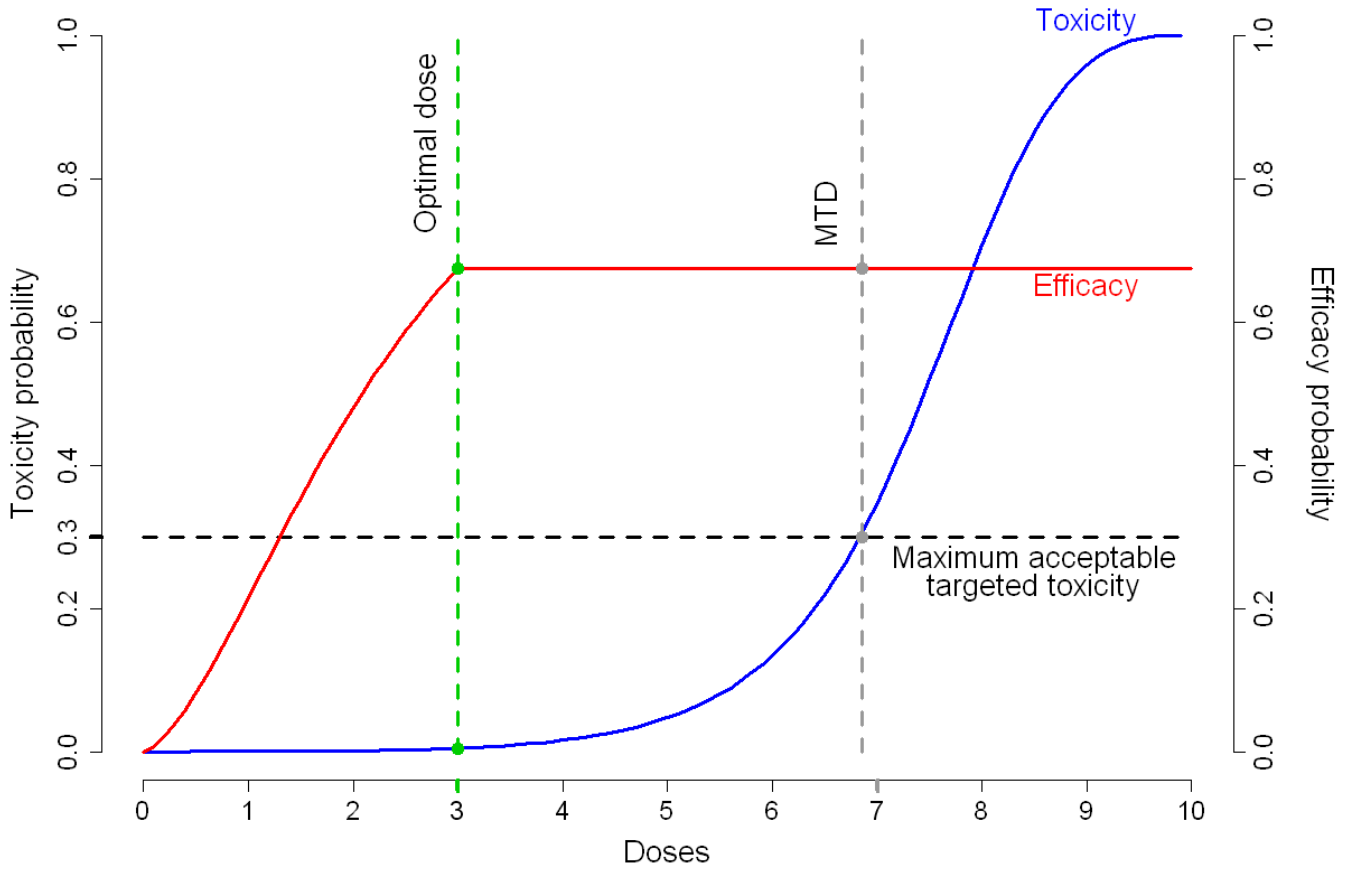
- **Two constraints**:
  - Ethical
    - Do not expose patients to dose levels with too high toxicity
    - Do not expose patients to ineffective dose levels
  - Small sample size: ≈30 patients

- **Consequences**:
  - Restricted number of dose levels
  - Adaptive design:
    - Re-estimation of the dose-toxicity after each cohort
    - Sequential dose allocation with dose administration rules

- **Algorithm-based/Model-based approaches**

Molecularly targeted agent

- Emergence of MTAs → Alternatives/complements to Cytotoxic
- Block the growth & spread of cancer by interfering with specific molecules
- Toxicity is increasing with the dose whereas efficacy is decreasing and then plateaus



COMBINATIONS

- Two or more drugs escalated within the same dose-finding clinical trial
- Example
  - Consider 2 drugs:

	Drug Combination					
Agent	d_1	d_2	d_3	d_4	d_5	d_6
A	54	67.5	75	79	84.5	89.5
B	6	6	6	5	7.5	9

  - Level d_3 may be more or less toxic than d_4
  - There are two possible simple orders (models).

$$M_1: d_1 \rightarrow d_2 \rightarrow d_3 \rightarrow d_4 \rightarrow d_5 \rightarrow d_6$$
$$M_2: d_1 \rightarrow d_2 \rightarrow d_4 \rightarrow d_3 \rightarrow d_5 \rightarrow d_6$$

- Combinations clinical trials need specific dose-escalation rule that take into account the ordering issue

PhD on IDEAL

Task 5.2. Adaptive two-stage designs in non-linear mixed effects models (Task Leader: INSERM, Partner: MUW, CTH)
One limitation of the optimal design approach for nonlinear model is the a priori knowledge needed. Adaptive design is an alternative increasingly developed for randomised clinical trial or dose-ranging studies, but merely applied in non-linear mixed effects model. Furthermore, two-stage designs are perhaps more efficient and more practical to implement in clinical settings than fully adaptive designs especially for small population groups. We wish to develop and evaluate by simulation two-stage designs in non-linear mixed effects model, with specific developments on use of prior information for first stage and development of stopping rules (in collaboration with Dr Sergei Leonov, AstraZeneca, US). Recommendations and good practices will be developed and corresponding R packages will be provided.

Task 5.3. Model uncertainty in designs for analyses of pivotal trials (Task Leader: INSERM, Partner: UU, PWR)
It is important to contribute to the dissemination of model based analysis of pivotal clinical trials in drug evaluation for small population groups. These approaches allow using all individual information recorded, and therefore to decrease sample sizes. Model based analysis is also more efficient than last observation carried forward to handle missing data because of dropouts [Siddiqui 2011]. The main limitations, as seen by health authorities, are the control of the type I error and a priori model specification.
Model averaging approaches is a good alternative. The idea of pre-specifying a number of pre-specified candidate models is already applied in drug development, for instance for dose-response studies in the MCPMod approach. Developing optimal design across a set of candidate non-linear mixed effects models will also be addressed (in collaboration with Prof. Gérard Pons, Cochin St Vincent de Paul Hospital, Paris, France). Specific methods will be proposed and implemented in R.

IDEAL

- Beginning: 1st December 2014

Direction: France MENTRE, INSERM UMR 1137

- Adaptive designs
- **Model averaging**
- MCPMod

Clinical trial simulation to evaluate power to compare the antiviral effectiveness of two hepatitis C protease inhibitors using nonlinear mixed effect models: a viral kinetic approach

BMC Med Res Methodol 2013:13-60.

Cédric Laouénan, Jérémie Guedj, France Mentré

IAME, UMR 1137, INSERM & University Paris Diderot, Sorbonne Paris Cité, Paris, France
AP-HP, Bichat hospital, Biostatistique,department, Paris, France

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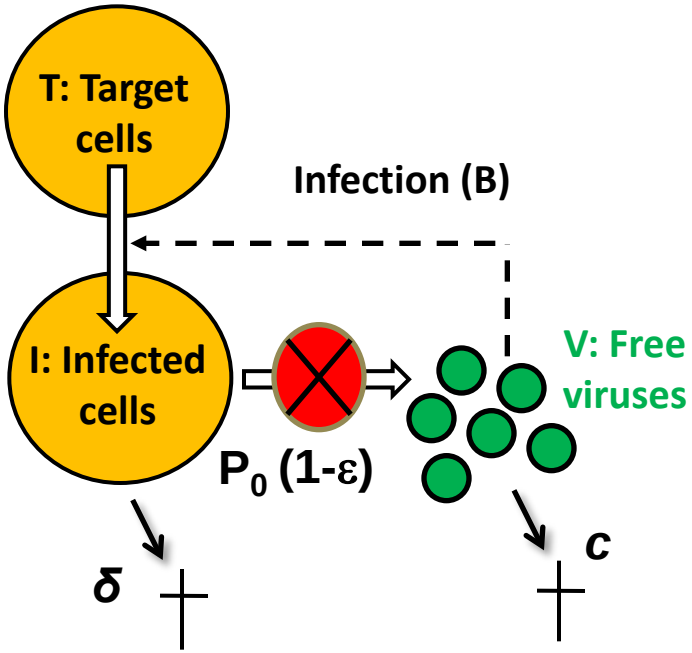
Hepatitis C Virus (HCV) viral kinetic modeling

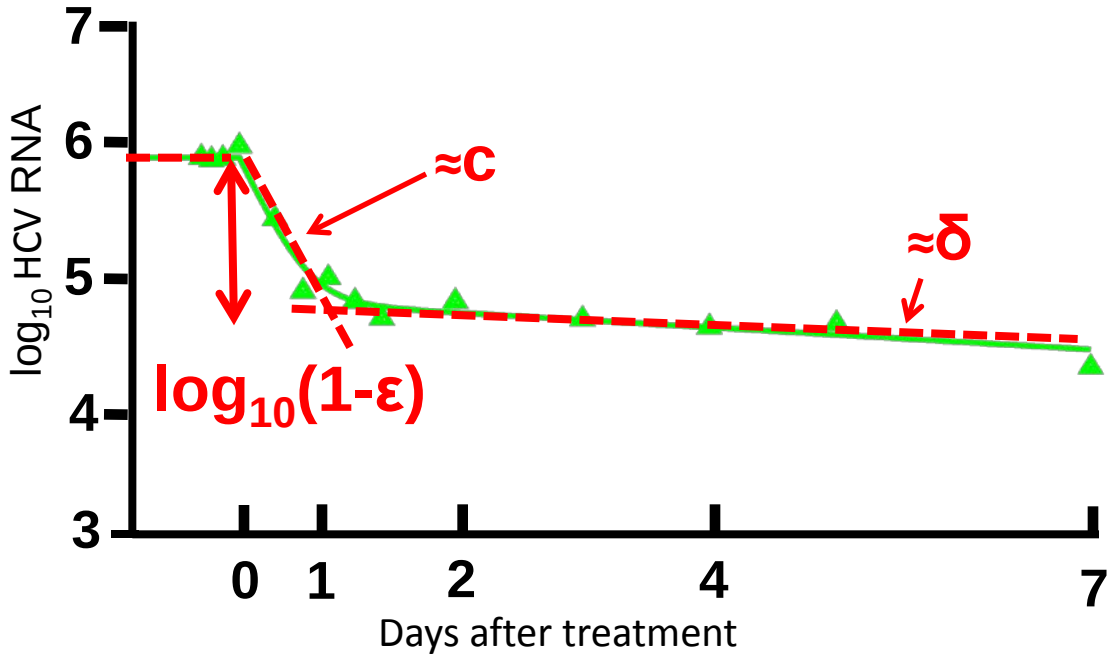
- Mathematical modeling of viral load (VL) decay after treatment initiation has brought critical insights for the understanding of the drug's mechanism of action and its antiviral effectiveness[1]

- Population approach with nonlinear mixed effect models (NLMEM): appropriate to estimate parameters of these models and their inter-patients variability

[1] *Neumann AU et al. Science (1998)*

Standard viral dynamic model[1]





ε = antiviral effectiveness (percentage of blockage of virion production)

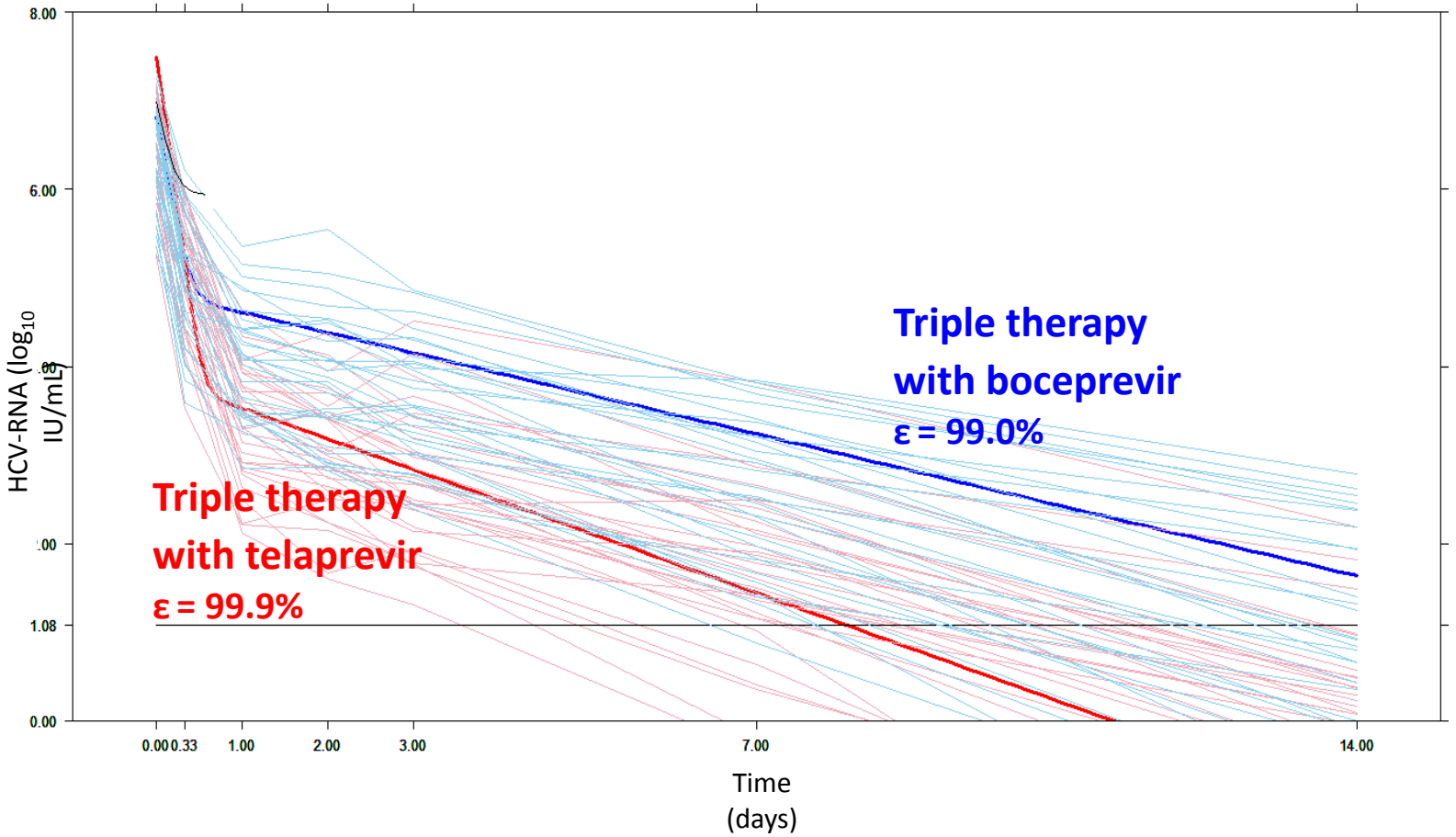
[1]*Neumann et al. Science (1998)*

Objectives

To evaluate by simulation the ability of the HCV dynamic model to detect a difference of antiviral effectiveness between two triple therapies with adequate power

Clinical trial simulation

- Designs:
  - n: number of VL (7 VL or 5 VL “sparce” in the first 14 days)
  - N: number of patients per triple therapie (10 to 100)
- 500 datasets were simulated for each design (R software v2.15)



Clinical trial simulation

- Population parameters were estimated using SAEM algorithm[1] in MONOLIX v4.2[2]
- **Test to compare the antiviral effectiveness between triple therapies:**
  - **By modeling:** Wald test on treatment effect $\beta = \text{logit}(\varepsilon^{telaprevir}) - \text{logit}(\varepsilon^{boceprevir})$
  - **Without modeling:** Wilcoxon test to compare VL differences between D0 and D14

Type I error

% of datasets where p-value < 0.05 under H_0

(assuming ε is similar for both triple therapies)

Power

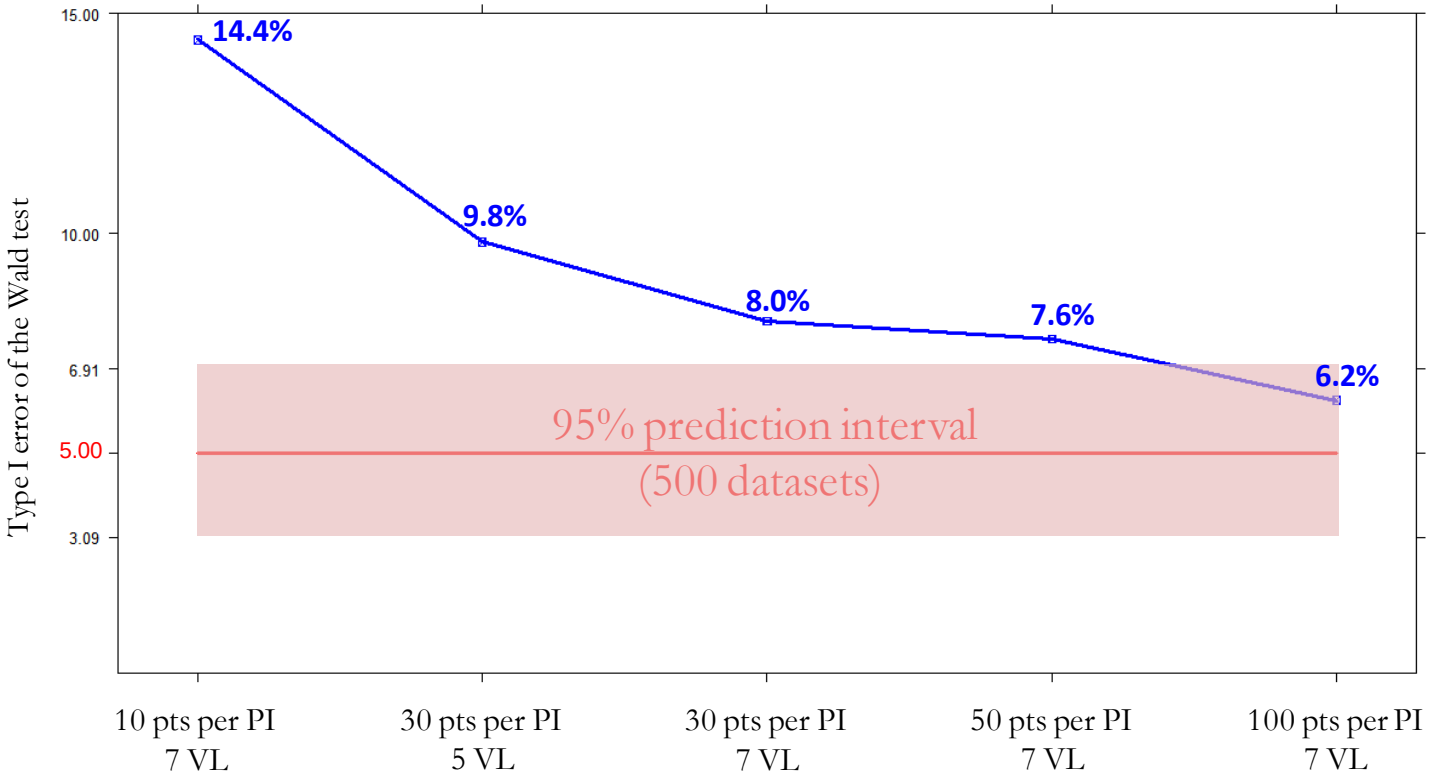
% of datasets where p-value < 0.05 under H_1*

(assuming ε is **NOT** similar both triple therapies)

*** threshold correction with permutation approach (inflation of the type I error[4])**

[1] *Delyon B et al. Ann Stat (1999)*
[2] *http://software.monolix.org*
[3] *Samson A et al. Comput Stat Data Anal (2006)*
[4] *Bertrand J et al. Biometrics (2012)*

Evolution of the type I error of the Wald test according to the study design



Type I error Wilcoxon is preserved

Power (%) to detect a difference of effectiveness between two triple therapies

Assuming $\varepsilon^{telaprevir} = 99.9\%$

Design	**10 patients per PI 7 VL**		
$\varepsilon^{boceprevir}$	**99.8%**	**99.5%**	**99.0%**
Wald test (**uncorrected**)	62.2	99.8	100
Wald test (**corrected**)	44.2	98.4	100
Wilcoxon test	6.6	11.2	26.8

Conclusion

- Viral dynamic model analyzed with NLMEM provided good power to compare antiviral effectiveness of two triple therapies, even with sparse initial sampling
- The Wald test is asymptotic: correction needed with small samples
- Unlike standard approach (Wilcoxon test), modeling approach (Wald test) provides a powerful tool to detect a difference in early viral kinetic profile

Perspectives in IDEAL

- Evaluation of corrections of the Wald test
- PFIM software[1]: R package for optimal design based on the Fisher Information Matrix for mixed models

→ prediction of power and number of subject needed using the Fisher Information Matrix for small sample size

- PFIM based on Wald test… include a correction in Fisher Information Matrix calculation?

[1] Bazzoli C, Retout S, Mentre F. Design evaluation and optimisation in multiple response nonlinear mixed effect models: PFIM 3.0. Comput Methods Programs Biomed. 2010;98(1):55-65.

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Model-based Power Calculations

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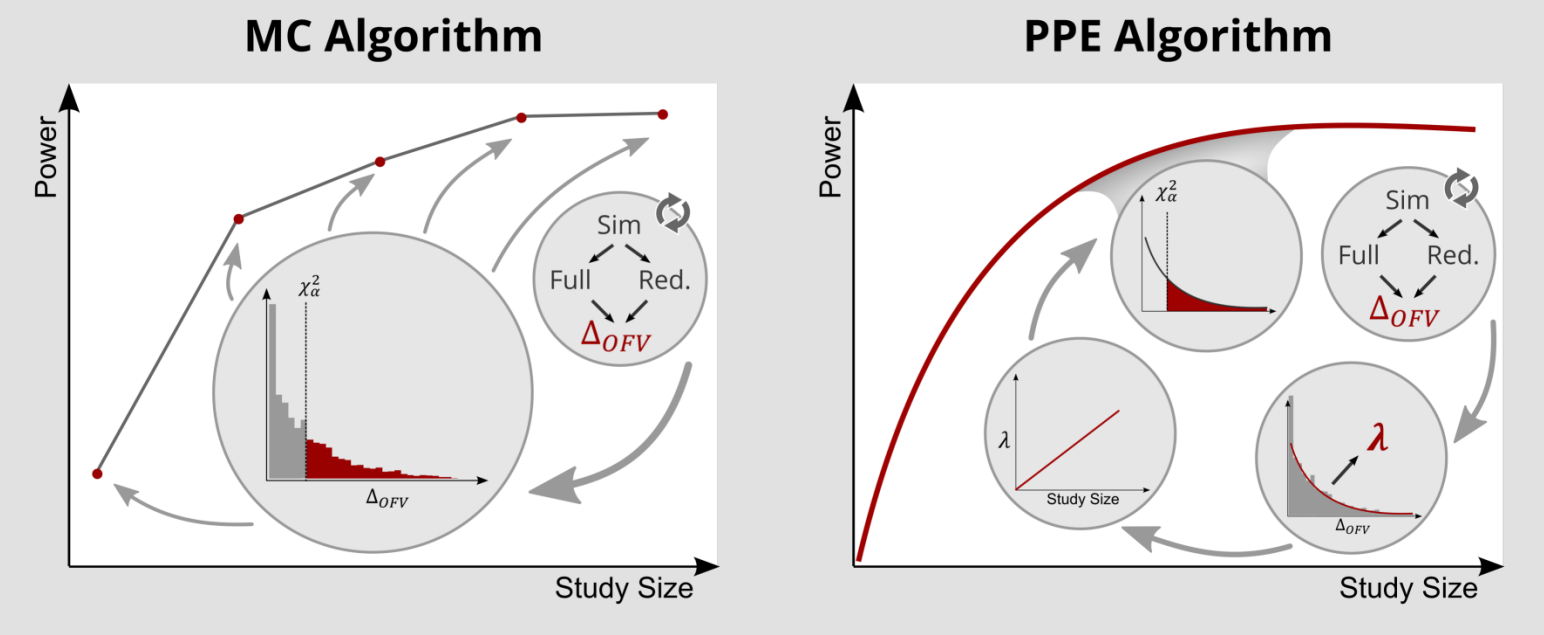
PHARMACOMETRICS RESEARCH GROUP,
DEPARTMENT OF PHARMACEUTICAL BIOSCIENCES,
UPPSALA UNIVERSITY

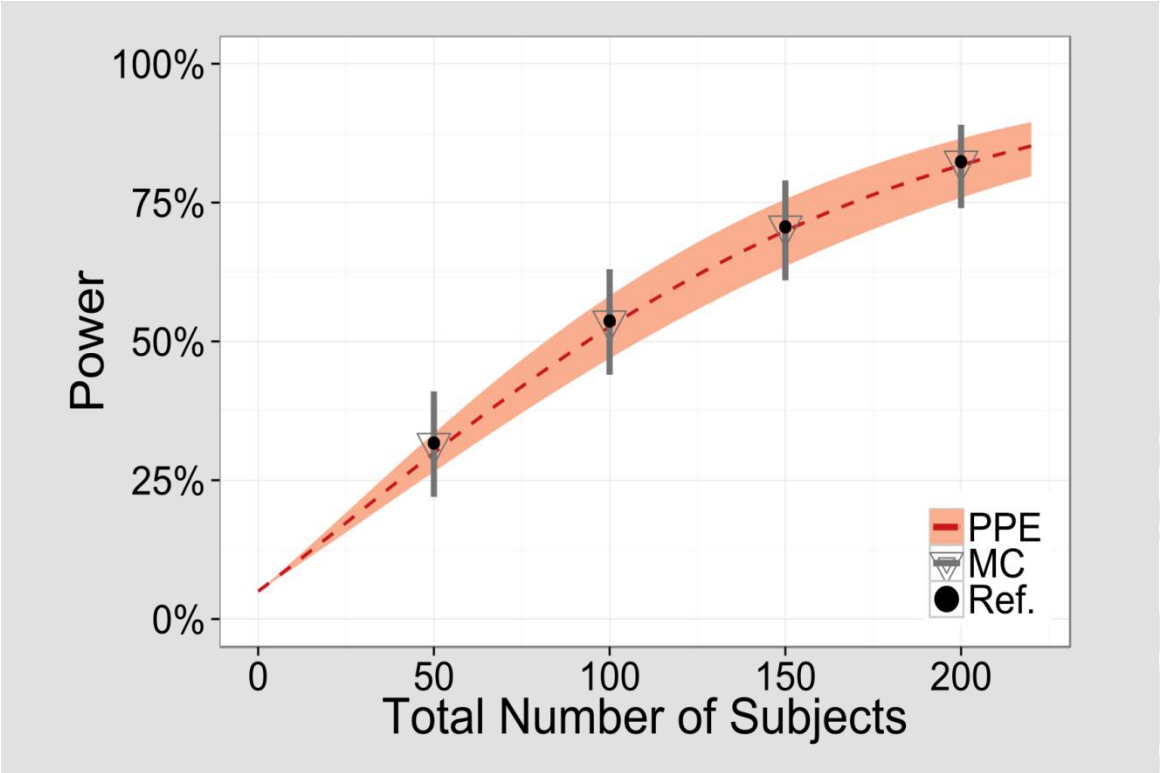
Schematic representation of two model-based power algorithms



MC: Monte-Carlo Simulations and Estimations
PPE: Parametric Power Estimation

S. Ueckert *et al*, *Accelerating Monte-Carlo Power Studies through Parametric Power Estimation*, PAGE 2014, Alicante, Spain

Power obtained from both algorithms and reference power for the disease progression model



S. Ueckert *et al*, *Accelerating Monte-Carlo Power Studies through Parametric Power Estimation*, PAGE 2014, Alicante, Spain

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Next step

- Apply and compare these methods in a rare disease scenario – for example Juvenile Idiopathic Arthritis

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Handling **uncertainty** when doing clinical trial simulations for small population groups

Anne-Gaëlle Dosne, PhD student

Young Scientists Meeting

Vienna 2014-06-30

Pharmacometrics Research Group

Department of Pharmaceutical Biosciences

Uppsala University

Sweden

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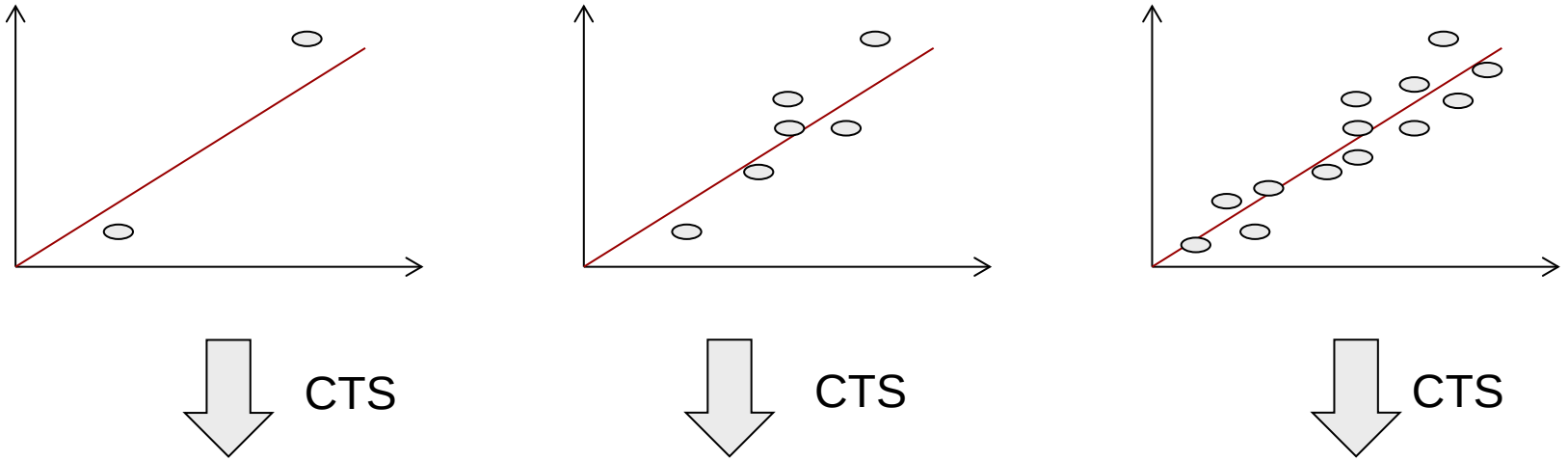
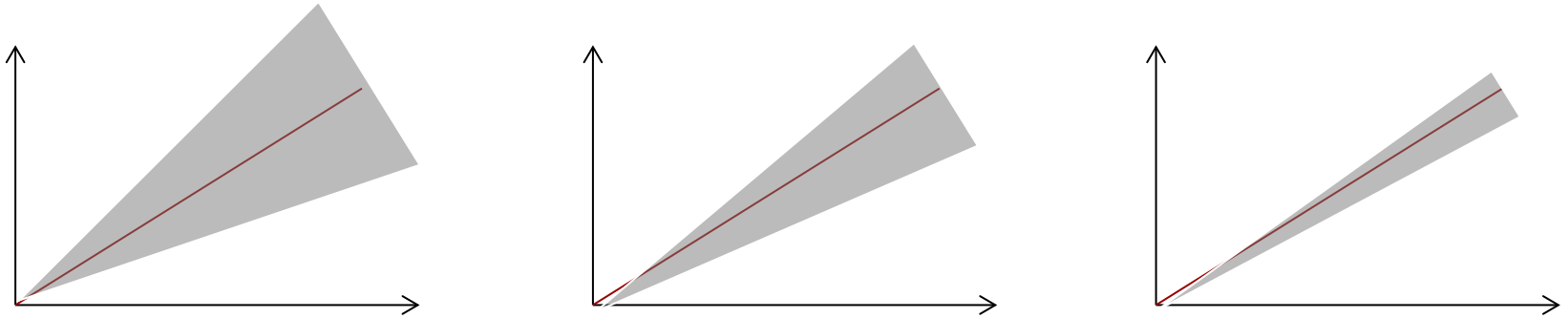
Model parameter uncertainty

AVAILABLE DATA



PREDICTED DATA



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Model parameter uncertainty

Covariance matrix

Bootstrap

FOCUS OF THIS RESEARCH

SIR

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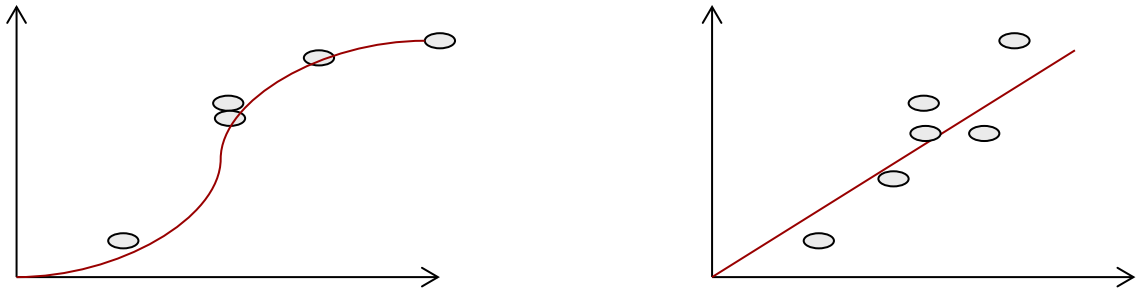
Model uncertainty

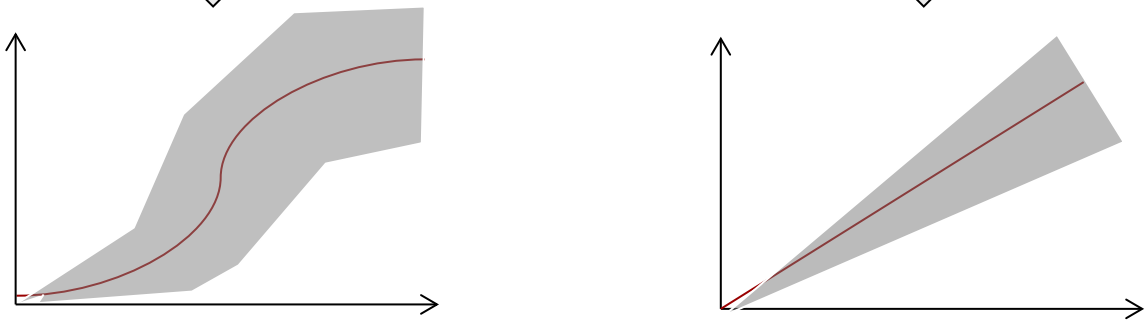
AVAILABLE DATA



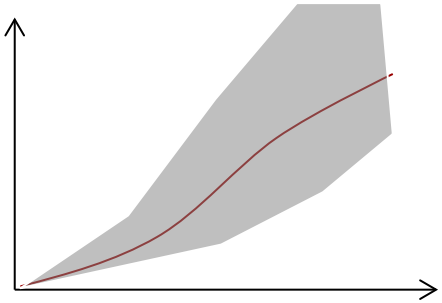
CTS

PREDICTED DATA

CTS



OR



MODEL AVERAGING

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Model uncertainty

FOCUS OF THIS RESEARCH

MODEL AVERAGING

Weighting strategy

Decision analysis in small population groups

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Who I am and what I do

- PhD student at Chalmers University, Gothenburg.
- Background in engineering physics.
- Working in the IDEAL project.
- WP9 = Decision analysis in small population groups.

WP9

Main goals of WP9:

- Improve the rational basis for decisions.
- Align stakeholder perspectives.

Stakeholders:

- Pharmaceutical companies
- Payers
- Regulatory agencies
- Physicians
- Patients

Stakeholders as decision makers

- Use Bayesian decision theory to find optimal decision rules.
- Model each stakeholder as a rational agent.
- Each agent has beliefs (a probability distribution).
- Each agent has preferences (an utility function).
- Optimal decision rules found by maximizing expected utility.

Formalisation of preferences

High level goals (preferences) must be defined by society.
Typical goals:

- Personalised health care.
- Adequate research in the area of rare diseases.

These must be translated into an utility function.

Aligning stakeholder perspectives

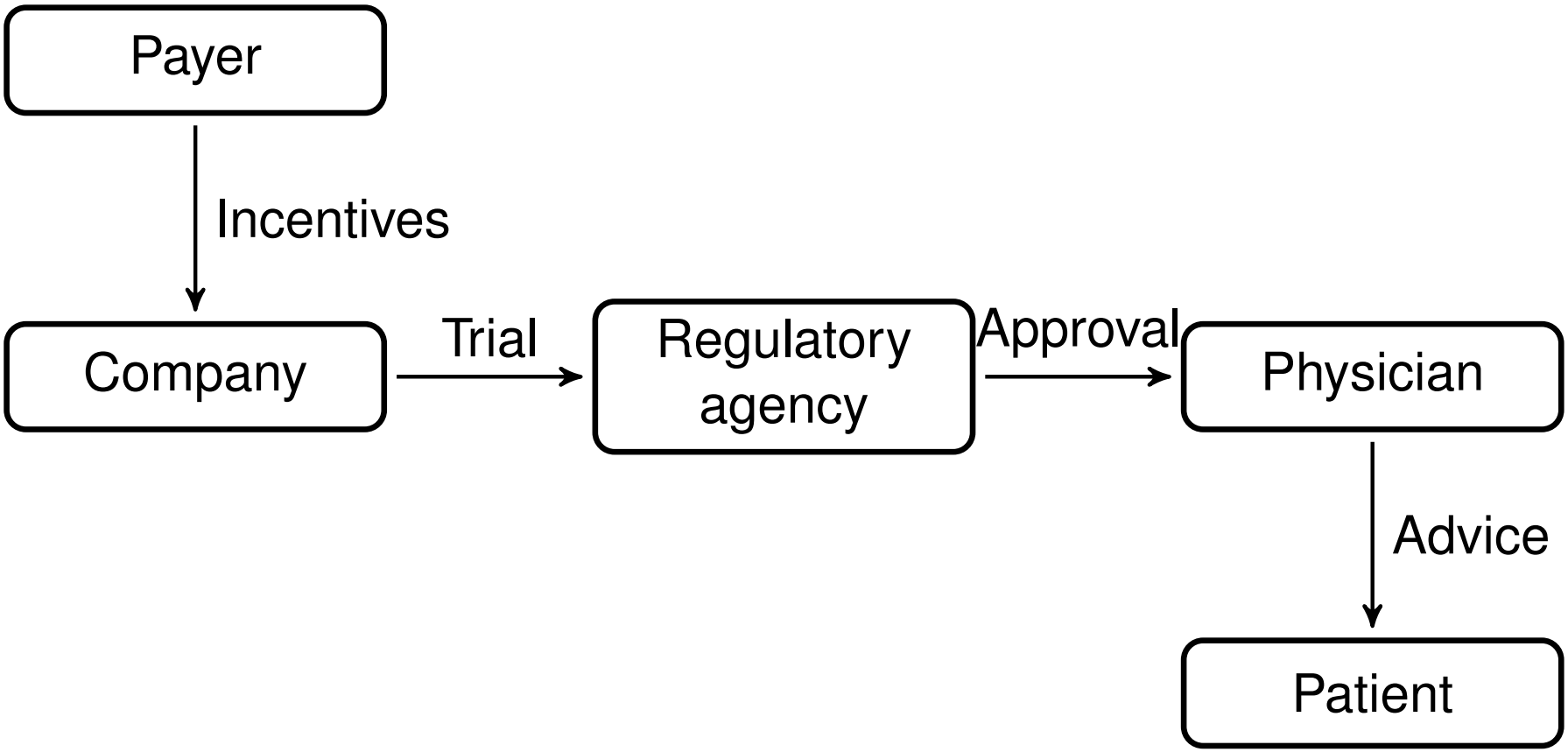
Strategy of analysis:

- Assume rationality (for the appropriate stakeholders).
- Create conditions that make certain decision rules rational.
- This will change the decision rules used by rational agents.

Some examples on how decision rules might be changed:

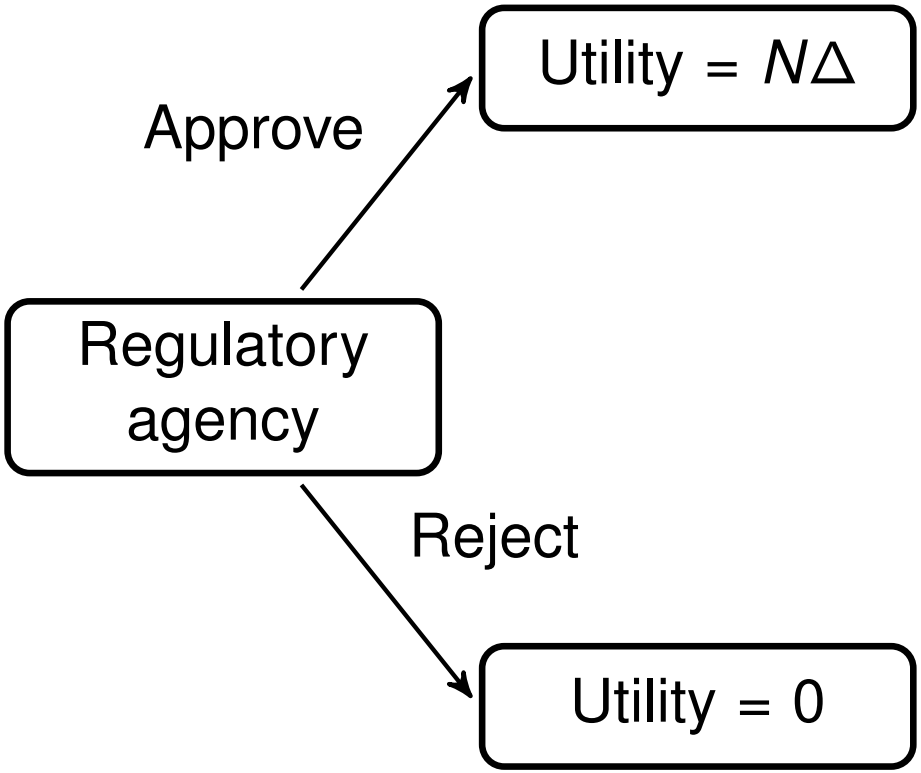
- Incentives to companies.
- Adjusted regulatory requirements.
- Alternative market rules.
- New governmental institutions.

Decision situation for multiple stakeholders



Decision situation for regulatory agency

N = number of patients adopting a new medication.
Δ = difference in effect between new and standard treatment.



Optimal to approve if and only if $\mathbb{E}(N\Delta \mid \text{Clinical results}) > 0$.

Research until now

Mainly questions about the decisions made by a company:

- Impact of regulatory requirements on optimal sample size?
- Impact of willingness to pay on optimal sample size?

Future research

- What regulatory requirements should be used?
- Are special requirements optimal for small populations (rare diseases)?
- What incentives (from society to private sector) are appropriate?

The end

Thanks for your attention!