Model-based Design of Dose-Finding Studies using Longitudinal Response Modelling

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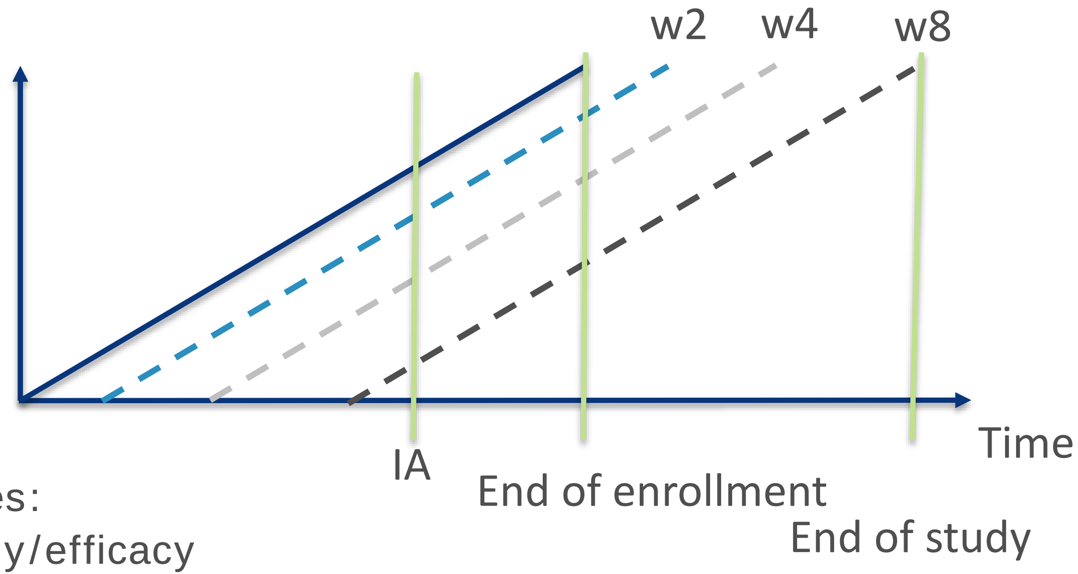
Melinda, *Tree of Life*
Melinda's artwork reflects her journey living with HIV.

janssen

Motivation



Use of interim analyses:

- Stop early for futility/efficacy
- Change sample size
- Change randomization, inclusion criteria…
- … but requires data for good decisions

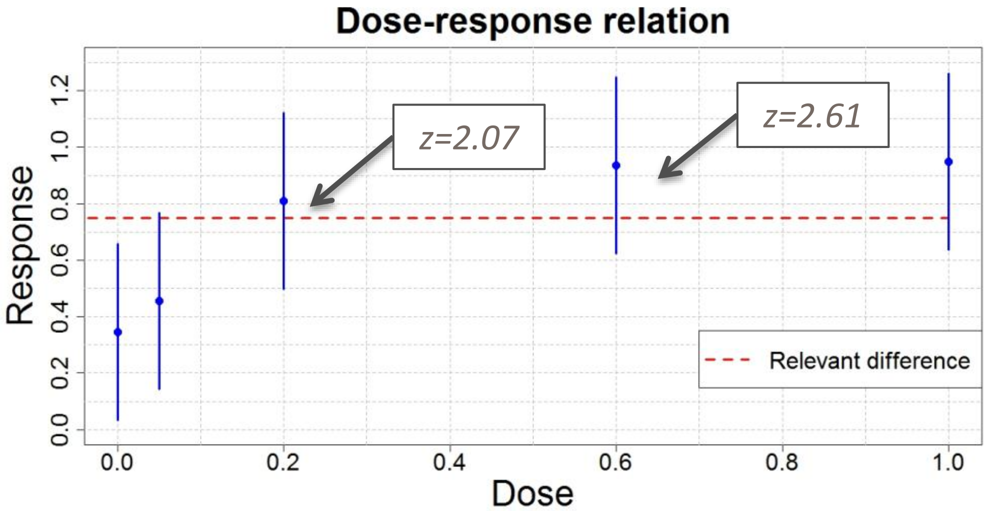
Motivation

Part of any study protocol in drug development: **Schedule of activities**

	V0 (Baseline)	V1 (2w)	V2 (4w)	V3 (8w)	V4 (12w)	V5 (24w)
Clinical evaluation	X	X	X	X	X	X
Blood pressure	X	X	X	X	X	X
Urinanalysis	X	X		X	X	X
PRO	X		X	X	X	X

- **Primary endpoint:** *Change from baseline in endpoint Y at week X.*
- **Data used for primary analysis**: Endpoint at „week X – Baseline“
- **Data at visits prior to week X**: Frequently not utilized in primary analysis

Dose Finding in Drug Development



Pairwise comparisons:

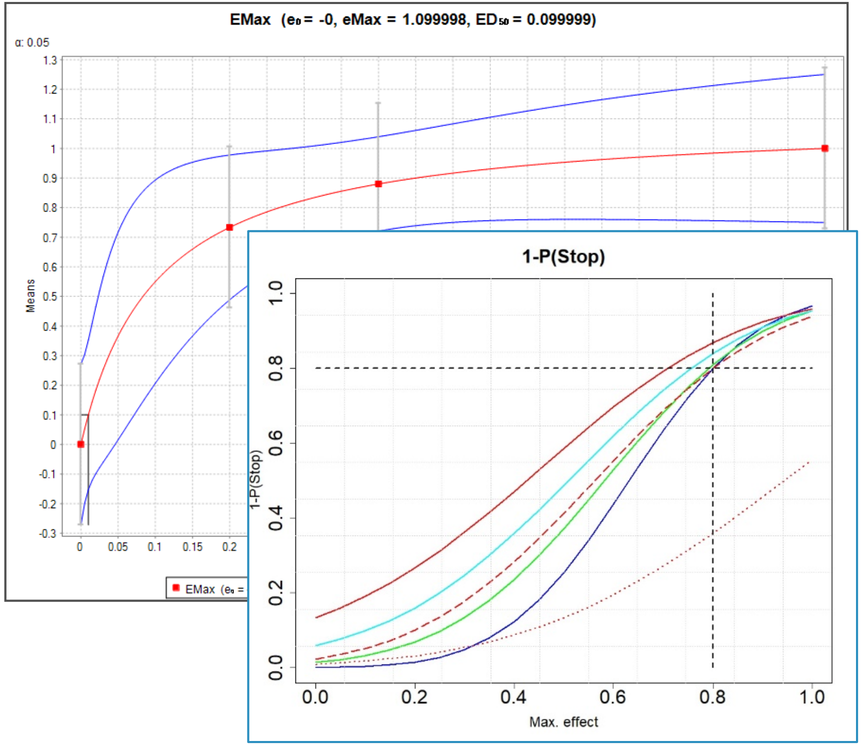
Arms	Reject
2	$z>1.96$
3	$z>2.21$
4	$z>2.35$
5	$z>2.44$
6	$z>2.51$

- Typical approach:
  - Compare each studied dose to placebo
  - … and finally find a reason to go with the highest safe dose.
- However, modelling seems to become slowly more popular

Longitudinal response modelling & DR modelling

Sharing of information through stat. models:

- $Y_{ij} = \eta(d_i, \beta_i, t_{ij}) + \epsilon_{ij}$, where
  - η: Longitudinal dose-response model
  - d_i: Dose assigned to patient i
  - β_i: Parameter vector for patient i
  - t_{ij}: Time of j-th assessment in patient i
  - ϵ_{ij}: error term



- Information is drawn from a model
- Model will bias analysis
- Error not fully controlled

Longitudinal response modelling & DR modelling

… continued: Modelling may increase error probability

- **Confirmatory decision making (confirm):**
  - Decision of not using modelling: understandable (at least for primary analysis)
- **Exploratory decision making (learn):**
  - Decision of not using modelling:
    - Tools are available to easily support modelling (e.g. from France, Andy or Sergei).
- **Interim decision making:**
  - Optimal timing of interim analysis severly depends on the amount of available information
  - Longitudinal modelling is of high interest to increase the information content.
  - Interim decisions may be made based on „exploratory“ techniques, while not invalidating the study (if properly actions taken into account)

Longitudinal dose response modelling

- … Finally starting
- Let: $Y_{ij} = \eta(d_i, \beta_i, t_{ij}) + \epsilon_{ij}$, where
  - η: Longitudinal dose-response model
  - d_i: Dose assigned to patient i
  - β_i: Parameter vector for patient i
  - t_{ij}: Time of j-th assessment in patient i
  - ϵ_{ij}: error term

Aim: Pick in an interim analysis the „correct“ dose for Phase III testing

- Problem:
  - At timing of interim analysis, not all patients will have reached endpoint…
  - … but we want to use their data anyway to support the decision making.

Longitudinal modelling approach

mODa contribution from Dragalin (2013): $Y_{ij} = [\eta(d_i, \beta) + b_i + \epsilon_{ij}]\gamma(t_{ij}, \theta)$

- η: Standard dose-response model with fixed parameters.
- d_i: Dose assigned to patient i
- $b_i \sim N(0, \sigma_\tau^2)$: Individual intercept for patient i (one per patient)
- $\epsilon_{ij} \sim N(0, \sigma_\epsilon^2)$: error term (one per observation / m per patient)
- t_{ij}: Time of j-th assessment in patient i
- $\gamma(t_{ij}, \theta)$: „Longitudinal correction “

Difference between both models:

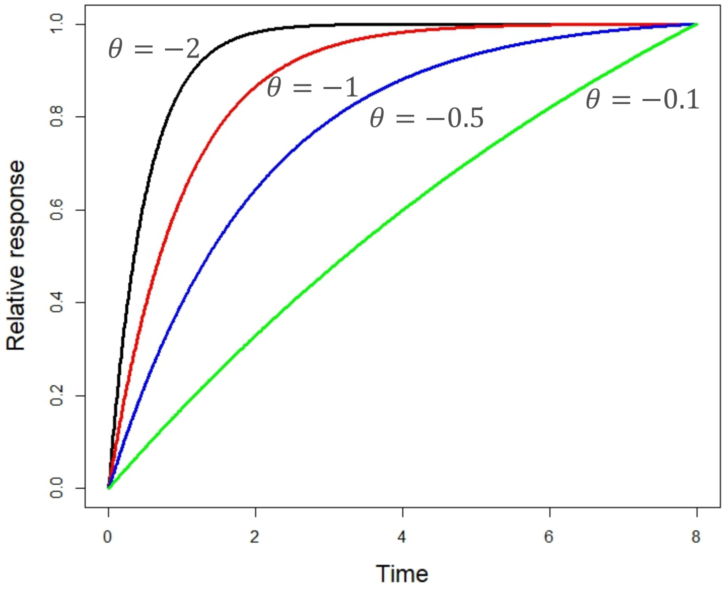
- $Y_{ij} = [\eta(d_i, \beta) + b_i + \epsilon_{ij}]\gamma(t_{ij}, \theta) \sim N\left(\eta(d_i, \beta)\gamma(t_{ij}, \theta), \gamma(t_{ij}, \theta)^2(\sigma_\tau^2 + \sigma_\epsilon^2)\right)$
- $Y_{ij} = \eta(d_i, \beta_i, t_{ij}) + \epsilon_{ij} \sim ???$

Dragalin (2013), Fu and Manner (2010)

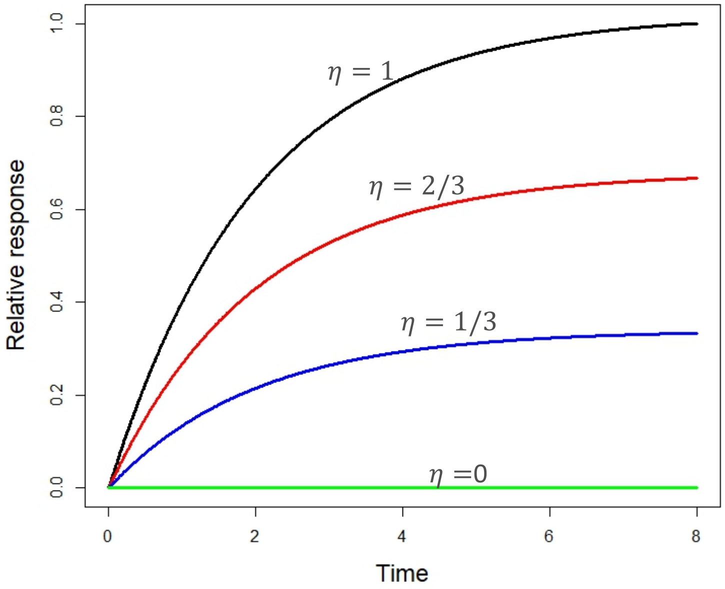
Longitudinal modelling approach

Longitudinal correction term $\gamma(t_{ij}, \theta) = \frac{1-\exp(t_{ij}\theta)}{1-\exp(T\theta)}$

Correction over time depending on θ



Correction over time depending on mean



Longitudinal modelling approach

Longitudinal correction term $\gamma\left(t_{ij},\theta\right) = \frac{1-\exp(t_{ij}\theta)}{1-\exp(T\theta)}$

- Implications:
  - At t_{ij}=0: $\gamma(0,\theta) = 0$ -> response and variance = 0
  - At t_{ij}=T: $\gamma(T,\theta) = 1$ ->
    - $Y_{ij} = \left[\eta(d_i,\beta\ ) + b_i + \epsilon_{ij}\right]\gamma(T,\theta) \sim N(\eta(d_i,\beta\ ),\sigma_\tau^2 + \sigma_\epsilon^2)$
    - $Y_{ij}|b_i = \eta(d_i,\beta\ ) + b_i + \epsilon_{ij} \sim N(\eta(d_i,\beta\ ),\sigma_\epsilon^2)$
  - In general:
    - $\Gamma \coloneqq diag(\gamma(t_{i1},\theta),\dots,\gamma(T,\theta))$, $\mathbf{1} \coloneqq (1,\dots,1)$
    - $\Sigma = \sigma_\epsilon^2\Gamma\ \Gamma +\ \sigma_\tau^2\Gamma\mathbf{1}\mathbf{1}^{\boldsymbol{T}}\Gamma$
    - $\mu = \eta(d_i,\beta\ )\Gamma\mathbf{1}^T$
    - $Y_i \sim N(\mu,\Sigma) = N(\mu(d_i,t_i;\beta,\theta),\Sigma(\theta,\sigma_\epsilon^2,\sigma_\tau^2))$

Model / Parameters

Model: $Y_i \sim N(\mu, \Sigma) = N(\mu(d_i, t_i; \beta, \theta), \Sigma(\theta, \sigma_\epsilon^2, \sigma_\tau^2))$

- Observations between individuals independent i=1,…,N
- Unknown parameters: $\beta, \theta, \sigma_\epsilon^2, \sigma_\tau^2$
- Fisher information for one observation ($Y_i \in \mathbb{R}^m$; $\vartheta := (\beta, \theta, \sigma_\epsilon^2, \sigma_\tau^2)$):

$$M_{i;\vartheta_k \vartheta_l}(d_i, t_i) = \frac{\partial \mu(d_i, t_i; \beta, \theta)}{\partial \vartheta_k} \Sigma(\theta, \sigma_\epsilon^2, \sigma_\tau^2)^{-1} \frac{\partial \mu(d_i, t_i; \beta, \theta)}{\partial \vartheta_l} + \frac{1}{2} tr\left[\Sigma^{-1} \frac{\partial \Sigma}{\partial \vartheta_k} \Sigma^{-1} \frac{\partial \Sigma}{\partial \vartheta_l}\right]$$

- Structure of information matrix:
- $M_i = \begin{pmatrix} A & B & 0 \\ B^T & C & D \\ 0 & D^T & E \end{pmatrix}$, A depends on d_i; B and C on d_i and t_i; D on t_i

Magnus and Neudecker (1988)

Design

- Design parameters:
  - Dose levels d_i
  - Assessment times $t_{i,j}$, j=1,…,m

$$M_i = \begin{pmatrix} A & B & 0 \\ B^T & C & D \\ 0 & D^T & E \end{pmatrix}$$

- Total information: $M_p \coloneqq \sum_{i=1}^{N} M_i\,(d_i, t_i)$
- Approximate population design:
- $\zeta \coloneqq \begin{pmatrix} d_1 & d_2 & d_3 & \cdots & d_{G-1} & d_G \\ (t_{11,\ldots,}t_{1m_1}) & (t_{21,\ldots,}t_{2m_2}) & (t_{31,\ldots,}t_{3m_3}) & \cdots & (t_{(G-1)1,\ldots,}t_{1m_{(G-1)}}) & (t_{G1,\ldots,}t_{1m_G}) \\ w_1 & w_2 & w_3 & \cdots & w_{(G-1)} & w_G \end{pmatrix}$
- Total information: $M_p \coloneqq \sum_{i=1}^{G} w_i M_i\,(d_i, t_i)$, $\sum_{i=1}^{G} w_i = 1$

Design criterion

- Target:
  - Estimate primary endpoint as good as possible, i.e.: $\eta(d_i, \beta\ )$
  - Requires good estimates of β
  - „Longitudinal model“$\gamma\left(t_{ij}, \theta\right)$ is not of interest
  - … some information required anyway for accurate interim insight in β
- Design criterion:
  - D_S optimality: $\Phi_S = \left(\det S\, M_p^{-1} S^T\right)^{1/q}$, with S a matrix targeting components for $\beta \in \mathbb{R}^q$
- Equivalence theorem:
  - Design is D_S-optimal, if:
  - $tr\left[\left(S M_p^{-1} S^T\right)^{-1} S M_p^{-1} M_i(d_i, t_i) M_p^{-1} S^T\right] \leq q$ for all (d_i, t_i) in the design set
- Equivalence theorem can be directly used for algorithmic design optimization

Atkinson et al. (2014)

Example

Linear dose-response model:

- $\eta(d_i, \beta) = \beta_0 + \beta_1 d$, admissible doses: d=0, 1, 2, ..., 10
- Each individual may be allocated to just one dose
- Endpoint: w24, assessment possible at: w2,w4,w8,w12,w16
- $\gamma(t_{ij}, \theta) = \frac{1-\exp(t_{ij}\theta)}{1-\exp(T\theta)}$, $\Delta_j = \left(\frac{Te^{\theta T}}{1-e^{\theta T}} - \frac{t_j e^{\theta t_j}}{1-e^{\theta t_j}}\right)$

Individual information matrix:

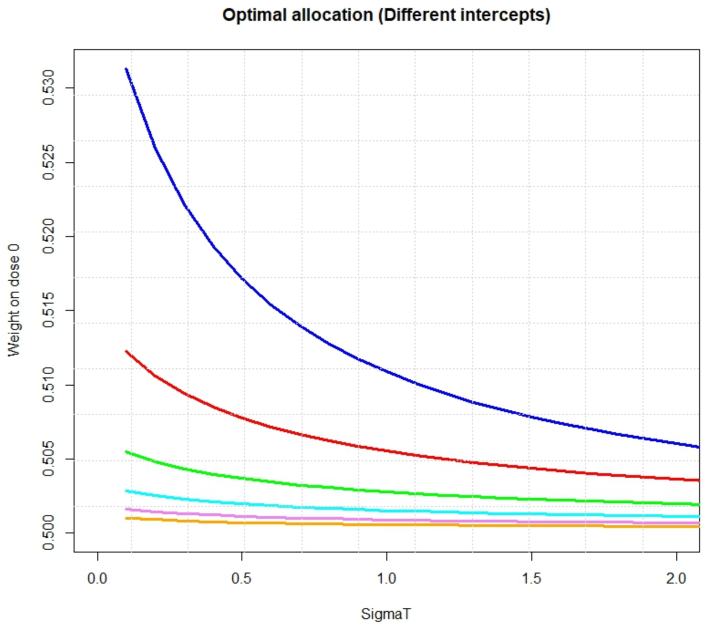
- $M_{i,\beta}(d_i, t_i) = \frac{m}{\sigma_\epsilon^2 + m\sigma_\tau^2}\begin{pmatrix} 1 & d_i \\ d_i & d_i^2 \end{pmatrix}$, $M_{i,\beta\theta}(d_i, t_i) = \frac{\sum_{j=1}^m \Delta_j}{\sigma_\epsilon^2 + m\sigma_\tau^2}\begin{pmatrix} 1 & d_i \\ d_i & d_i^2 \end{pmatrix}\begin{pmatrix} \beta_0 \\ \beta_1 \end{pmatrix}$
- $M_{i,\theta}(d_i, t_i) = \frac{\sum_{j=1}^m \Delta_j^2}{\sigma_\epsilon^2}(\eta(d_i, \beta)^2 + \cdots) - \cdots$

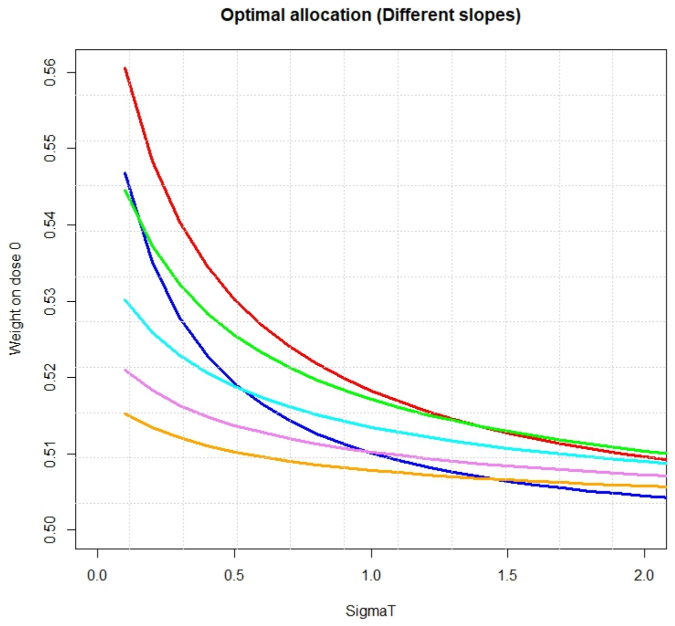
To make long story short: FIM depends even in linear model on $\beta_0, \beta_1, \theta\ (through\ \Delta_j), \sigma_\epsilon^2, \sigma_\tau^2$

➢ Designs possibly just locally optimal

Example

- If allowed to, optimal design will pick all visits
- Optimal allocation in this case:





Cost functions

Increased complexity: individual measurements come also with some costs

- Consider instead cost efficient design, i.e. introduce:
- $C(\zeta) = (c_1 + c_2 \sum_{j=1}^{G} w_j m_j)$
- Fixed cost for individual: c_1
- Fixed cost per visit c_2

Cost normalized information matrix:

$$\frac{M_p(\zeta)}{C(\zeta)} := \frac{\sum_{i=1}^{G} w_i M_i\,(d_i, t_i)}{C(\zeta)} = \sum_{i=1}^{G} w_i \frac{c_1 + c_2 m_i}{C(\zeta)} \frac{M_i\,(d_i, t_i)}{c_1 + c_2 m_i}$$

- Note:
- $\sum_{i=1}^{G} w_i \frac{c_1+c_2 m_i}{C(\zeta)} = \frac{1}{C(\zeta)} \sum_{i=1}^{G} w_i (c_1+c_2 m_i) = \frac{1}{C(\zeta)} (c_1 + c_2 \sum_{i=1}^{G} w_i m_i) = 1$

Dragalin and Fedorov (2006)

Cost functions

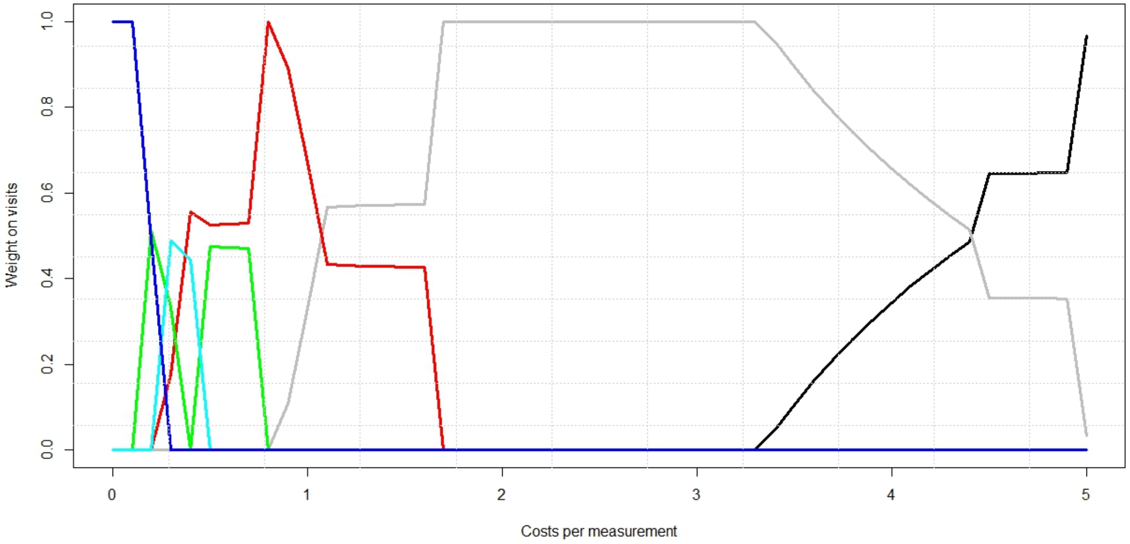
Optimality criterion:

$$\Phi_{C;S} = \left(\det C(\zeta) S\,(M_p^{-1}) S^T\right)^{1/q} \to min$$

- Equivalence theorem:
  - Design is optimal, if:
  - $tr\left[\left(SM_p^{-1}S^T\right)^{-1} SM_p^{-1}M_i(d_i, t_i)M_p^{-1}S^T\right]\frac{C(\zeta)}{c_1+c_2m_i} \leq q$ for all (d_i, t_i) in the design set
- Standard design optimization algorithms may be utilized
  - Resulting optimal weights: $\widehat{w}_i^* = w_i^* \frac{c_1+c_2m_i}{C(\zeta)}$
  - Actual design weights deduced from $\widehat{w}_i^*$

Example

- Depending on the costs for measurements, number of visits will be restricted
- Consider here: costs for individual=1



m	Colour
1	Black
2	Grey
3	Red
4	Green
5	Cyan
6	Blue

Summary / Conclusions / Outlook

- The heteroscedasticity has an influence on the design
- In the considered model, the impact on efficiency seems to be small
- However, the model is likely not the model typically to be used

For logistical constraints:

- Restriction to one visit schedule more likely to be relevant
- Inclusion of recruitment assumptions in design optimization to:
  - Optimization of visits for maximum information at interim could be handled similarily

Thank you for your attention!

References

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