OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG

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Individuals Differ: Implications on the Design of Experiments

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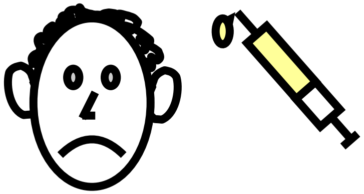
Outline

Prologue: Short introduction

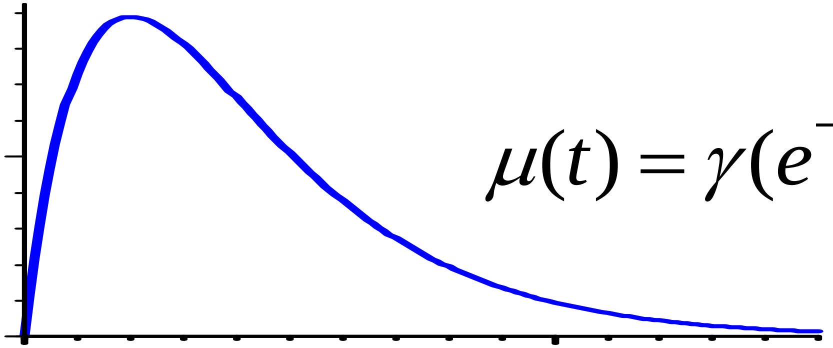
1. Linear models
2. Linear mixed models
3. Non-linear models
4. Non-linear mixed models
5. Miscellaneous

Prologue: Short introduction

- <u>Example: Pharmacokinetics</u>

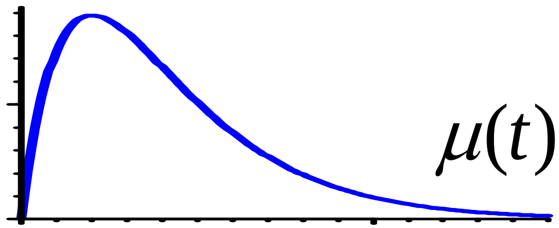


  - measure the concentration of a drug in s.o.'s blood over time

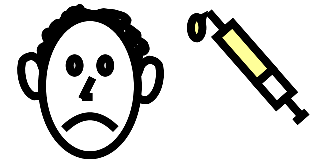


$$\mu(t) = \gamma(e^{-\alpha t} - e^{-\beta t})$$

Example: Pharmacokinetics



$$\mu(t) = \gamma(e^{-\alpha t} - e^{-\beta t})$$



- aim:

  estimate AUC (area under the curve),

  $c_{\max}$ (maximal concentration) etc.

$$Y_j(t_j) = \gamma(\exp(-\alpha \cdot t_j) - \exp(-\beta \cdot t_j)) + \varepsilon_j$$

---

optimal times $t_1, \ldots, t_n$ depend on parameters

General model

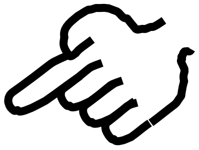
measurements $Y_1,\ldots,Y_n$ at settings $t_1,\ldots,t_n$

$$Y_j(t_j) = \mu(t_j;\boldsymbol{\beta}) + \varepsilon_j$$

resp. mean response

$$\mathrm{E}(Y_j(t_j)) = \mu(t_j;\boldsymbol{\beta})$$

- response function μ
- parameter $\boldsymbol{\beta} = (\beta_1,\ldots,\beta_p)$



General model

measurements $Y_1,...,Y_n$ at settings $t_1,...,t_n$

$$Y_j(t_j) = \mu(t_j;\boldsymbol{\beta}) + \varepsilon_j$$

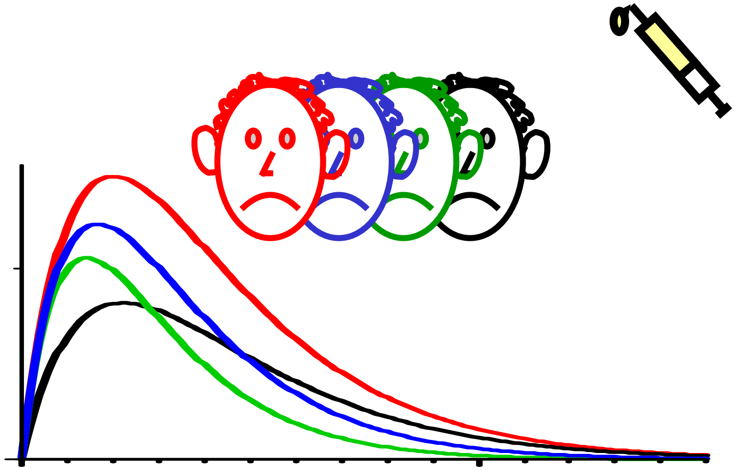
resp. mean response

$$\mathrm{E}(Y_j(t_j)) = \mu(t_j;\boldsymbol{\beta})$$

- observations uncorrelated
- + assumptions on $\mathrm{Var}(Y_j)$
  or distribution of Y_j

Random coefficients

- each individual
  has its **own** curve



- population parameters
- individual prediction
- variance components

1. Linear models

- linear response $\mu(t;\boldsymbol{\beta}) = \mathbf{f}(t)^{\mathsf{T}}\boldsymbol{\beta}$

$$Y_j(t_j) = \mathbf{f}(t_j)^{\mathsf{T}}\boldsymbol{\beta} + \varepsilon_j$$

random error

observation
j=1,...,n

explanatory variable

ε_j i.i.d.
$\mathrm{Var}(\varepsilon_j) = \sigma^2$

- regression functions $\mathbf{f} = (f_1, \ldots, f_p)$
- parameter $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_p)$

Vector notation

$$\mathbf{Y} = \begin{pmatrix} Y_1 \\ \vdots \\ Y_n \end{pmatrix} = \mathbf{F}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$$

$$\mathrm{Cov}(\mathbf{Y}) =$$

$$\mathrm{Cov}(\boldsymbol{\varepsilon}) = \sigma^2 \mathbf{I}_n$$

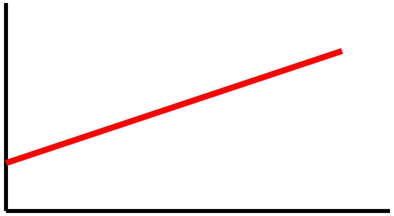
- design matrix

$$\mathbf{F} = \begin{pmatrix} \mathbf{f}(t_1)^\mathsf{T} \\ \vdots \\ \mathbf{f}(t_n)^\mathsf{T} \end{pmatrix}$$

$(n \times p)$

Linear regression

$$Y_j(t_j) = \beta_1 + \beta_2 \cdot t_j + \varepsilon_j$$



- dimension $p = 2$
- regression functions $f_1(t) \equiv 1,\ f_2(t) = t$

- design matrix $(2 \times n)$

$$\mathbf{F} = \begin{pmatrix} 1 & t_1 \\ 1 & t_2 \\ \vdots & \vdots \\ 1 & t_n \end{pmatrix}$$

Estimation

- <u>Gauss Markov Theorem</u>

$$\hat{\boldsymbol{\beta}} = \left(\mathbf{F}^{\mathsf{T}}\mathbf{F}\right)^{-1}\mathbf{F}^{\mathsf{T}}\mathbf{Y}$$

least squares

best linear unbiased estimator for $\boldsymbol{\beta}$

- covariance matrix

$$\mathrm{Cov}(\hat{\boldsymbol{\beta}}) = \sigma^2\left(\mathbf{F}^{\mathsf{T}}\mathbf{F}\right)^{-1}$$

- "information matrix"

$$\mathbf{M} = \frac{1}{\sigma^2}\mathbf{F}^{\mathsf{T}}\mathbf{F} = \frac{1}{\sigma^2}\sum_{j=1}^{n}\mathbf{f}(t_j)\mathbf{f}(t_j)^{\mathsf{T}}$$

Estimation

- <u>Normal theory</u>

maximum likelihood

$$\hat{\boldsymbol{\beta}} = \left(\mathbf{F}^{\top}\mathbf{F}\right)^{-1}\mathbf{F}^{\top}\mathbf{Y}$$

best unbiased estimator for $\boldsymbol{\beta}$

- Fisher information matrix

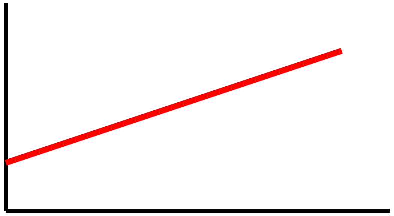
$$\mathbf{M} = \mathrm{Cov}(\mathit{score\ fct.}) = \frac{1}{\sigma^2}\sum_{j=1}^{n}\mathbf{f}(x_j)\mathbf{f}(x_j)^{\top}$$

- covariance matrix

$$\mathrm{Cov}(\hat{\boldsymbol{\beta}}) = \mathbf{M}^{-1}$$

Linear regression

$$Y_j(t_j) = \beta_1 + \beta_2 \cdot t_j + \varepsilon_j$$



- dimension $p = 2$
- regression functions $f_1(t) \equiv 1, \; f_2(t) = t$

- information matrix (2×2)

$$\mathbf{F}^{\mathrm{T}}\mathbf{F} = \begin{pmatrix} n & \sum t_j \\ \sum t_j & \sum t_j^2 \end{pmatrix} = \sum \begin{pmatrix} 1 \\ t_j \end{pmatrix} \begin{pmatrix} 1 & t_j \end{pmatrix}$$

Design

- "exact design" $(t_1,\ldots,t_n)$
- information matrix

$$\mathbf{M}(t_1,\ldots,t_n) = \frac{1}{\sigma^2}\sum_{j=1}^{n}\mathbf{f}(t_j)\mathbf{f}(t_j)^{\mathsf{T}}$$

- aim: choose $t_1,\ldots,t_n$ from design region T

to minimise $\mathbf{M}^{-1}$ $= \mathrm{Cov}(\hat{\boldsymbol{\beta}})$

resp. $\mathrm{v}(t) = \mathbf{f}(t)^{\mathsf{T}}\mathbf{M}^{-1}\mathbf{f}(t)$ prediction variance

Design criteria

- minimise

D: $\det \mathbf{M}^{-1}$

A: $\operatorname{trace} \mathbf{M}^{-1}$

$\mathbf{c}$: $\mathbf{c}^{\mathrm{T}} \mathbf{M}^{-1} \mathbf{c}$

IMSE: $\int_T \mathbf{f}(t)^{\mathrm{T}} \mathbf{M}^{-1} \mathbf{f}(t) \, \mathrm{d}t$

G: $\max_{t \in T} \mathbf{f}(t)^{\mathrm{T}} \mathbf{M}^{-1} \mathbf{f}(t)$

Design criteria

- interpretation

  D: volume of confidence ellipsoid

  A: average variance

  $\mathbf{c}$: variance of $\mathbf{c}^T\boldsymbol{\beta}$

  IMSE: average prediction variance

  G: maximal prediction variance

- <u>Linear regression</u>

$$Y_j(t_j) = \beta_1 + \beta_2 \cdot t_j + \varepsilon_j \qquad 0 \le t \le 1$$

$$\mathbf{M} = \frac{1}{\sigma^2}\begin{pmatrix} n & \sum t_j \\ \sum t_j & \sum t_j^2 \end{pmatrix}$$

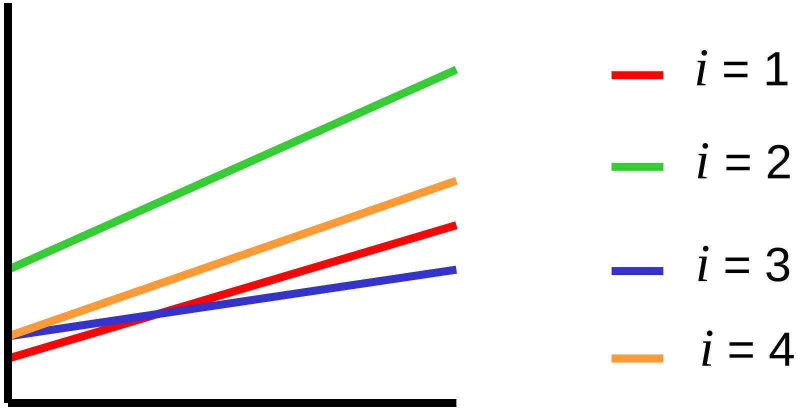
- observations at $t = 0$ and $t = 1$

D-, G-and $IMSE$-optimal	50 % at $t = 1$
A-optimal	≈ 40 % at t = 1

2. Linear mixed models

- each individual has its **own** response curve

octodon degus



- individual responses follow a common model

Hierarchical model

- individual level

individual "parameter"

$$Y_{ij} = \mathbf{f}(t_{ij})^{\top}\mathbf{b}_i + \varepsilon_{ij}$$

individual
$i=1,\ldots,n$

replication
$j=1,\ldots,m_i$

explanatory variable

error

$$\varepsilon_{ij} \sim \mathrm{N}(0, \sigma^2)$$

- population level

independent

$$\mathbf{b}_i \sim \mathrm{N}_p(\boldsymbol{\beta}, \mathbf{D})$$

population parameter

variance components

Individual Observational Vector

$$\mathbf{Y}_i = \mathbf{F}_i \boldsymbol{\beta} + \mathbf{F}_i (\mathbf{b}_i - \boldsymbol{\beta}) + \boldsymbol{\varepsilon}_i$$

individual design matrix

- individual covariance matrix

$$\mathbf{V}_i = \mathbf{F}_i \mathbf{D} \mathbf{F}_i^{\mathsf{T}} + \sigma^2 \mathbf{I}_{m_i}$$

observations are **correlated**

- e.g. random intercept

equal correlations

$$\mathbf{V}_i = \sigma_\mu^2 \mathbf{1}_{m_i} \mathbf{1}_{m_i}^{\mathsf{T}} + \sigma^2 \mathbf{I}_{m_i}$$

Estimation of population parameters

- least squares (ML for normal errors)

$$\hat{\boldsymbol{\beta}} = \left(\sum_{i=1}^{n} \mathbf{F}_i^\top \mathbf{V}_i^{-1} \mathbf{F}_i\right)^{-1} \sum_{i=1}^{n} \mathbf{F}_i^\top \mathbf{V}_i^{-1} \mathbf{Y}_i$$

- covariance matrix

$$\mathrm{Cov}(\hat{\boldsymbol{\beta}}) = \left(\sum_{i=1}^{n} \mathbf{F}_i^\top \mathbf{V}_i^{-1} \mathbf{F}_i\right)^{-1}$$

- note

$$(\mathbf{F}_i^\top \mathbf{V}_i \mathbf{F}_i)^{-1} = (\mathbf{F}_i^\top \mathbf{F}_i)^{-1} + \mathbf{D}$$

additive decomposition

Single group designs

- all individuals at the same time points

$$m_i \equiv m$$
$$t_{ij} \equiv t_j$$

$$\mathbf{F}_i \equiv \mathbf{F}, \ \mathbf{V}_i \equiv \mathbf{V}$$

- estimation

$$\hat{\boldsymbol{\beta}} = \left(\sum_{i=1}^{n} \mathbf{F}^{\top} \mathbf{F} \right)^{-1} \sum_{i=1}^{n} \mathbf{F}^{\top} \mathbf{Y}_i$$

does not require the knowledge of $\mathbf{D}$ (WLS=OLS)

Covariance in single group designs

$$\mathrm{Cov}(\hat{\boldsymbol{\beta}}) = \frac{1}{n}\left(\sigma^2\left(\mathbf{F}_1^{\mathsf{T}}\mathbf{F}_1\right)^{-1} + \mathbf{D}\right)$$

- covariance decomposes additively into
  - » covariance in the model without random effects $(\mathbf{D} = \mathbf{0})$
  - » dispersion $\mathbf{D}$ of the parameter

- single group designs are optimal within the class of weighted approximate designs (equivalence theorems)

Linear criteria

A, IMSE, $\mathbf{c}$

- minimise

$$\text{trace}\left(\mathbf{L}\left(\sigma^2\left(\mathbf{F}^\top\mathbf{F}\right)^{-1}+\mathbf{D}\right)\mathbf{L}^\top\right)$$

constant !

$$=\sigma^2\,\text{trace}\left(\mathbf{L}\left(\mathbf{F}^\top\mathbf{F}\right)^{-1}\mathbf{L}^\top\right)+\underbrace{\text{trace}\left(\mathbf{L}\mathbf{D}\mathbf{L}^\top\right)}$$

- result:

optimal designs in the model

without random effects

remain optimal with random effects

✓

D- and G-criteria

- minimise

$$\det\left(\sigma^2\left(\mathbf{F}^\top\mathbf{F}\right)^{-1}+\mathbf{D}\right)$$

D-criterion

$$>\det\left(\sigma^2\left(\mathbf{F}^\top\mathbf{F}\right)^{-1}\right)+\det(\mathbf{D})$$

- resp.

$$\sup_t\left(\mathbf{f}(t)^\top\left(\sigma^2\left(\mathbf{F}^\top\mathbf{F}\right)^{-1}+\mathbf{D}\right)\mathbf{f}(t)\right)$$

G-criterion

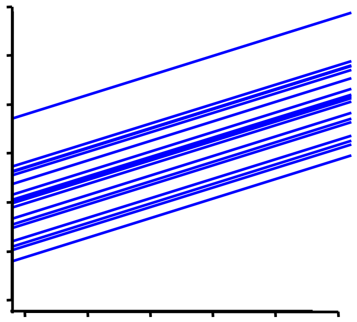
$$<\sigma^2\sup_t\left(\mathbf{f}(t)^\top\left(\mathbf{F}^\top\mathbf{F}\right)^{-1}\mathbf{f}(t)\right)+\sup_t\left(\mathbf{f}(t)^\top\mathbf{D}\mathbf{f}(t)\right)$$

- optimal designs may differ ! ⇒ examples

Random intercept (random blocks)

- parallel individual curves

$$Y_{ij} = a_i + \mathbf{f}(t_{ij})^\top \boldsymbol{\beta} + \varepsilon_{ij}$$



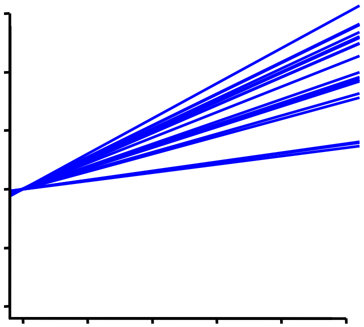
- G- and D-optimal designs

  do not depend on σ_a^2 ✓

Random treatment effect

- common baseline
  (quite unrealistic)

$$Y_{ij} = \mu + b_i t_{ij} + \varepsilon_{ij}$$

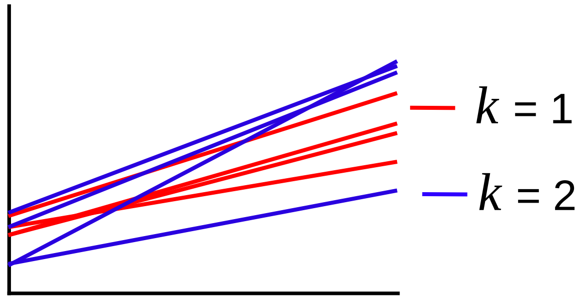


- D-and G-optimal design differ

	observations at baseline	
	σ_b^2 small	σ_b^2 large
D-criterion	$m/2$	$m-1$
G-criterion	$m/2$	1
$IMSE$-criterion	$m/2$	$m/2$

Several treatments

- individuals
  nested in groups



- random intercept (baseline)
  - information may percolate through from one group to the other: more observations at baseline
  - optimal designs depends on σ_a^2
  - standard designs are quite efficient

3. Non-linear models

- general model equation

$$Y(t) = \mu(t;\boldsymbol{\beta}) + \varepsilon$$

parameter: $\boldsymbol{\beta}$

observation: $Y(t)$

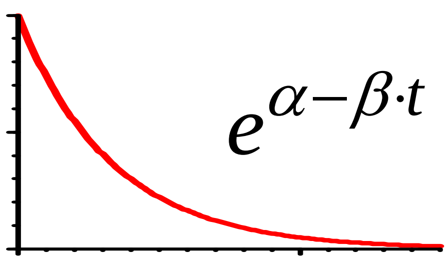
response function: μ

explanatory variable: t

error: ε

- resp. mean response

$$\mathrm{E}(Y(t)) = \mu(t;\boldsymbol{\beta})$$



Linearised model

$$Y_{\boldsymbol{\beta}_0}(t) = \mathbf{f}_{\boldsymbol{\beta}_0}(t)^{\mathsf{T}}\boldsymbol{\beta} + \varepsilon$$

- linearised regression function

$$\mathbf{f}_{\boldsymbol{\beta}_0}(t) = \frac{\partial \mu(t;\boldsymbol{\beta}_0)}{\partial \boldsymbol{\beta}}$$

at $\boldsymbol{\beta}_0 = \boldsymbol{\beta}$

Homoscedastic errors

$$Y_{\boldsymbol{\beta}}(t) = \mathbf{f}_{\boldsymbol{\beta}}(t)^{\mathsf{T}} \boldsymbol{\beta} + \varepsilon$$

- equal variances

$$\mathrm{Var}(Y_{\boldsymbol{\beta}}(t)) = \sigma^2$$

- information matrix

$$\mathbf{M}_{\boldsymbol{\beta}}(t_1, \ldots, t_n) = \frac{1}{\sigma^2} \sum \mathbf{f}_{\boldsymbol{\beta}}(t_j) \mathbf{f}_{\boldsymbol{\beta}}(t_j)^{\mathsf{T}}$$

depends on β

Local optimality

- information matrix depends on $\boldsymbol{\beta}$

$\Longrightarrow$ optimal design may depend on $\boldsymbol{\beta}$

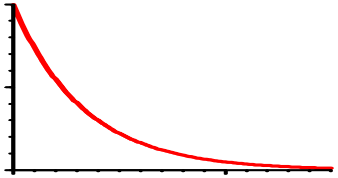
- local approach

  design locally D-optimal at $\boldsymbol{\beta}$

  $\Longleftrightarrow$ design minimises $\det \mathbf{M}_{\boldsymbol{\beta}}^{-1}$

- alternatives $\Rightarrow$ weighted, minimax criteria

Example: Exponential decay



$$Y(t) = e^{\alpha - \beta \cdot t} + \varepsilon \qquad t \geq 0$$

$\boldsymbol{\beta} = (\alpha, \beta)^{\mathsf{T}}$

- linearisation

$$Y(t) \approx e^{\alpha_0 - \beta_0 \cdot t} \cdot (\alpha - \beta t) + \varepsilon$$

$\mathbf{f}_{\boldsymbol{\beta}}(t) = e^{\alpha - \beta \cdot t}(1, -t)^{\mathsf{T}}$

- information matrix

$$\mathbf{M}_{\boldsymbol{\beta}} = \frac{e^{2\alpha}}{\sigma^2} \sum e^{-2\beta \cdot t_j} \begin{pmatrix} 1 & -t_j \\ -t_j & t_j^2 \end{pmatrix}$$

- *D*-optimal design

$$t_1^* = 0, \;\; t_2^* = 1/\beta$$

4. Non-linear mixed models

- individual response specified by common model

$$Y_{ij} = \mu(t_{ij}, \mathbf{b}_i) + \varepsilon_{ij}$$

individual i=1,...,n

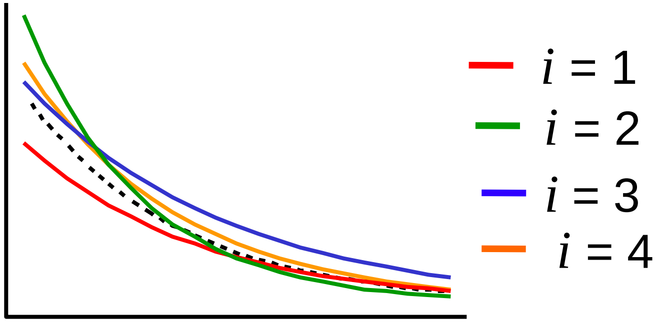
replication j=1,...,m_i

explanatory variable

error

$$\varepsilon_{ij} \sim \mathrm{N}(0, \sigma^2)$$

- individual curves



4. Non-linear mixed models

- hierarchical modelling

$$Y_{ij} = \mu(t_{ij}, \mathbf{b}_i) + \varepsilon_{ij}$$

individual "parameter"

individual $i=1,\ldots,n$

replication $j=1,\ldots,m_i$

explanatory variable

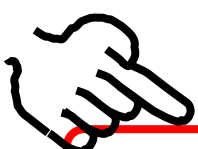
error

$\varepsilon_{ij} \sim \mathrm{N}(0, \sigma^2)$

- individual parameters:

independent

$$\mathbf{b}_i \sim \mathrm{N}_p(\boldsymbol{\beta}, \mathbf{D})$$



population parameter

variance components

Linearised model

$$\mathbf{Y}_{i,\boldsymbol{\beta}_0} = \mathbf{F}_{i,\boldsymbol{\beta}_0}\boldsymbol{\beta} + \mathbf{F}_{i,\boldsymbol{\beta}_0}(\mathbf{b}_i - \boldsymbol{\beta}) + \boldsymbol{\varepsilon}_i$$

- linearised design matrix

$$\mathbf{F}_i = \mathbf{F}_{i,\boldsymbol{\beta}} = \left(\frac{\partial \mu(t_{ij}, \boldsymbol{\beta})}{\partial \boldsymbol{\beta}^{\mathsf{T}}}\right)_{j=1,\ldots,m_i}$$

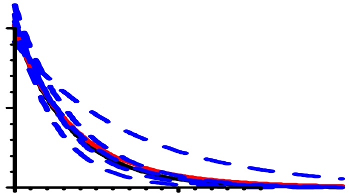
at $\boldsymbol{\beta}_0 = \boldsymbol{\beta}$

- linearised covariance matrix $\mathbf{V}_i = \mathbf{F}_i \mathbf{D} \mathbf{F}_i^{\mathsf{T}} + \sigma^2 \mathbf{I}_{m_i}$

$$\sqrt{n}(\hat{\boldsymbol{\beta}}_{\mathrm{ML}} - \boldsymbol{\beta}) \overset{?}{\to} \mathrm{N}_p\left(\mathbf{0}, \lim\left(\frac{1}{n}\sum_{i=1}^{n} \mathbf{F}_i^{\mathsf{T}} \mathbf{V}_i^{-1} \mathbf{F}_i\right)^{-1}\right)$$

$\mathbf{M}_{\boldsymbol{\beta}}$

Example: Exponential decay



$$Y_{ij}(t_j) = e^{a_i - b_i \cdot t_j} + \varepsilon_{ij} \qquad t \geq 0$$

- linearisation

$$Y_{ij}(t) \approx e^{\alpha_0 - \beta_0 \cdot t} \cdot (\alpha - \beta t) + e^{\alpha_0 - \beta_0 \cdot t} \cdot ((a_i - \alpha) - (b_i - \beta) t) + \varepsilon$$

- information matrix for estimation of $\boldsymbol{\beta}$

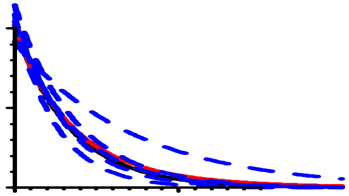
$$\mathbf{M}_{\boldsymbol{\beta}} = \left(\left(\frac{e^{2\alpha}}{\sigma^2} \sum e^{-2\beta \cdot t_j} \begin{pmatrix} 1 & -t_j \\ -t_j & t_j^2 \end{pmatrix} \right)^{-1} + \mathbf{D} \right)^{-1}$$

- D-optimal design

$$t_1^* = 0, \;\; t_2^* > 1/\beta$$

depends on $\mathbf{D}$

Example: Exponential decay, prediction



$$Y_{ij}(t_j) = e^{a_i - b_i \cdot t_j} + \varepsilon_{ij} \qquad t \geq 0$$

- linearisation

$$Y_{ij}(t) \approx e^{\alpha_0 - \beta_0 \cdot t} \cdot (\alpha - \beta t) + e^{\alpha_0 - \beta_0 \cdot t} \cdot ((a_i - \alpha) - (b_i - \beta) t) + \varepsilon$$

- information for individual prediction of $\mathbf{b}_i$

$$\ln \det \mathbf{M}_{\boldsymbol{\beta}} \propto \ln \det \left(\frac{e^{2\alpha}}{\sigma^2} \sum e^{-2\beta \cdot t_j} \begin{pmatrix} 1 & -t_j \\ -t_j & t_j^2 \end{pmatrix} + \mathbf{D}^{-1} \right) + \ldots$$

- D-optimal design

$$t_1^* = 0, \;\; t_2^* < 1/\beta$$

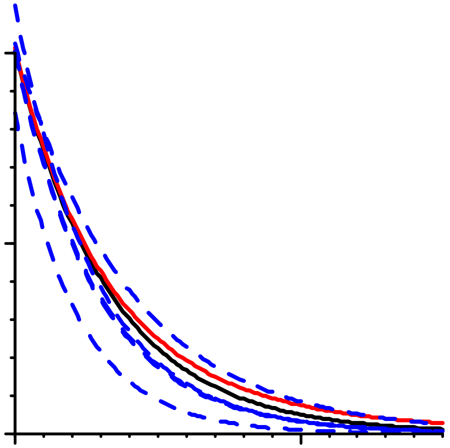
depends on $\mathbf{D}$

Example: Exponential decay

- parameterisation matters

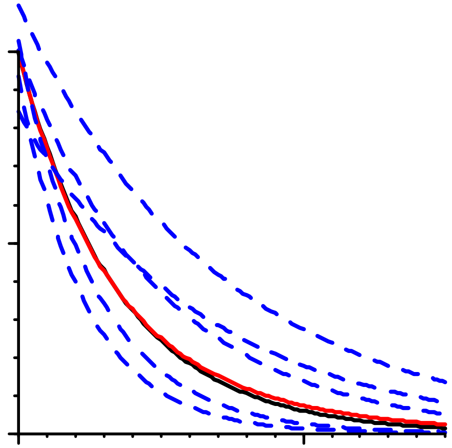
normal

$$Y_{ij}(t_j) = e^{a_i - b_i t_j} + \varepsilon_{ij}$$



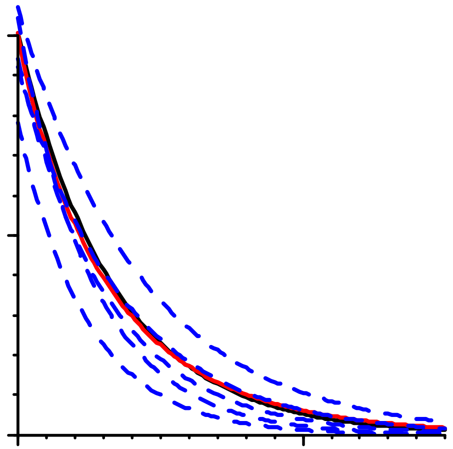
lognormal

$$Y_{ij}(t_j) = e^{a_i - e^{b_i} t_j} + \varepsilon_{ij}$$



inverse normal

$$Y_{ij}(t_j) = a_i e^{-t_j / b_i} + \varepsilon_{ij}$$



individual curves: mean curve $\neq$ typical curve

- impact on optimal designs ?

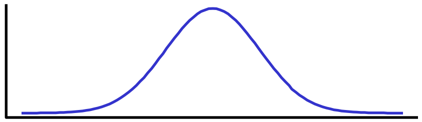
5. Miscellaneous

- locally optimal designs
  - » depend on parameter β (unknown!) and/or $\mathbf{D}$
  - » may badly perform,
    if parameter β (or $\mathbf{D}$) is misspecified

- possible solutions
  - » averaged criteria ("Bayes", pseudo-Bayes)
    according to a weight ("prior") on β (or $\mathbf{D}$)
  - » minimax criteria (maximin efficiency)
    guarding against least favourable values of β (or $\mathbf{D}$)

Weighted (averaged) criteria

- criterion is weighted by a distribution π on $\boldsymbol{\beta}$ (or $\mathbf{D}$) ("prior")



e.g. weighted D-criterion: $-\int \ln(\det(\mathbf{M}_{\boldsymbol{\beta}}))\,\pi(d\boldsymbol{\beta})$

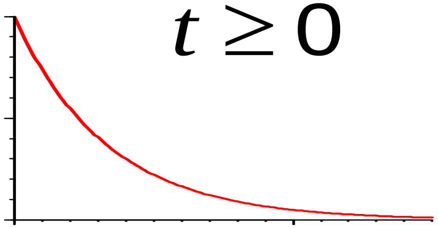
- optimal design depends on the "prior"

- analytical evaluation often not possible
  - » numerical integration
  - » need for good algorithms

Example: Exponential decay

$$Y(t) = e^{\alpha - \beta \cdot t} + \varepsilon$$

$t \geq 0$



- homoscedastic:

$$\mathrm{Var}(Y(t)) = \sigma^2$$

- D-optimal design w.r.t. π

mean of β

$$t_1^* = 0, \;\; t_2^* = 1 \Big/ \int \beta \, \pi(\mathrm{d}\beta)$$

if the dispersion of π is small

Minimax criteria

- minimise the criterion for the worst value of $\boldsymbol{\beta}$ (or $\mathbf{D}$) on a parameter region B (region of interest)

  e.g. maximin D-efficiency

$$-\min_{\boldsymbol{\beta} \in B} \left(\frac{\det(\mathbf{M}_{\boldsymbol{\beta}})}{\det(\mathbf{M}^*_{\boldsymbol{\beta}})} \right)^{1/p}$$

  » standardisation of the criterion with respect to the locally optimal design

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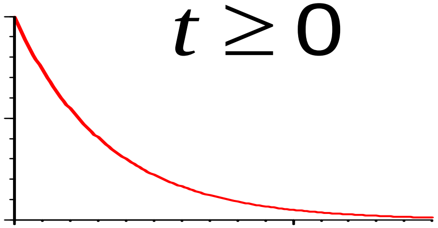
- optimal design depends on the region

Example: Exponential decay

$$Y(t) = e^{\alpha - \beta \cdot t} + \varepsilon$$



$t \geq 0$

- homoscedastic:

$$\operatorname{Var}(Y(t)) = \sigma^2$$

- maximin D-efficient design on $B = [\beta_1, \beta_2]$

$$t_1^* = 0, \; t_2^* = 1/\beta_2$$

worst case

Further problems

- model specification
  - parameterisation
  - distribution of random coefficients
  - (conditional) distribution of observations
  - correlation structure within individuals
  - sparse sampling

- **reliable** asymptotic theory
  - alternative estimation methods (quasi likelihood ...)

- **reliable** software for data analysis

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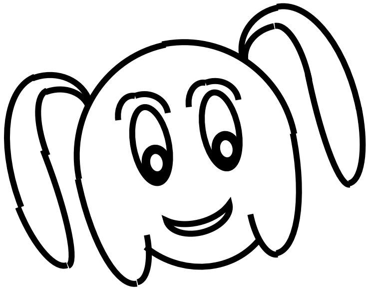

Thank you !

Some kind of conclusion

At the beginning we were confused about the problem

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Now we are confused on a higher level

Disclaimer

By purpose, there has not been given any reference to the literature, because, due to the vast amount, mentioning some would have meant omitting others, which were equally or even more important.

Some (incomplete) list of literature may be available from the author.