DESIGNING A DOSE-RESPONSE STUDY ANALYSED BY NONLINEAR MIXED EFFECTS MODELS

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BACKGROUND

- **Dose-response studies**: Importance of identifying the right dose
  - Two main analysis approaches: multiple comparisons between doses or modelling [1]
  - Modelling: more flexible, increasingly performed in drug development
  - Specific case: several doses evaluated for each patient

  ⇒ **Modelling through nonlinear mixed effects models (NLMEM)**
- **Importance of choice of design**
  - Trial with one dose/patient: methods to choose robust efficient design for estimating the minimum effective dose already proposed [2]
  - Trial with several doses/patient: how to choose appropriate population design ? (the number of patients ? the number of doses ? which doses ?)
  - Impact on the study results (precision of parameter estimates, power of test,...)
- **Design evaluation and optimisation in NLMEM**
  - Simulations : time consuming, limited number of designs evaluated
  - Population Fisher information matrix (M_F)
    - M_F for NLMEM, using first order approximation of the model [3,4]
    - Implementation in R function PFIM [5,6] and in other software

MOTIVATING EXAMPLE & OBJECTIVE

- **Motivating example: Dose-response trial with several doses/patient** [7]
  - **Emax model**

$$E = E0 + \frac{Emax \times dose}{D50 + dose}$$

  - **Parameters** $E0 = 5,\ Emax = 30,\ D50 = 500$ mg
  - **Modelling through NLMEM**
    - Exponential model for random effects with standard deviation of inter patient variability = 0.7 for $E0, Emax$ and 0.3 for $D50$
    - Additive model for random error with standard deviation of random error = 2

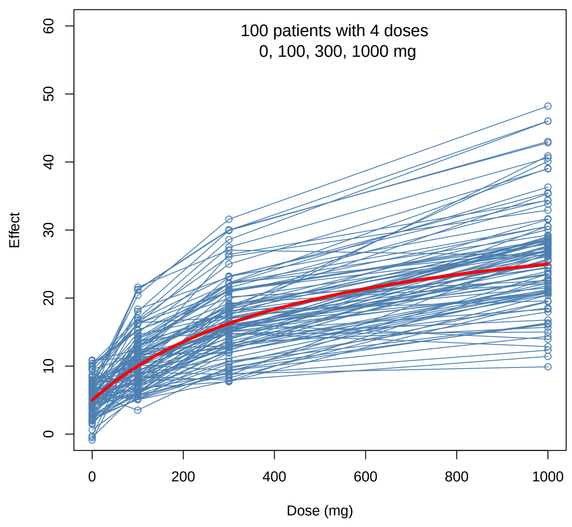

Figure 1: Example of a dose-response trial

  - **Comparison between two treaments A and B in N patients**
    - Two parallel group design: N/2 patients receiving treament A, N/2 patients receiving treament B which decreases D50 by 50% compared to A
    - Inclusion of a discrete covariate β_{D50} in NLMEM ⇒ $\beta_{D50} = \log(0.5)$

- **Objective: To design this dose-reponse study using PFIM 3.2**
  1. **To study the influence of design on criterion and precision of D50 estimation**
  2. **To study the influence of covariate on D50 on design optimisation and to evaluate the power of the comparison Wald test for this covariate effect**

METHODS

Designing with PFIM 3.2 [5]

- Computing population Fisher information matrix M_F by linearisation of the model [3,4]
- Prediction of standard errors (SE) or relative standard errors (RSE) for population parameters from the diagonal terms of M_F^{-1}
- Optimisation of designs with Fedorov-Wynn algorithm [8]

1. Evaluation of the influence of design on criterion and precision of D50 estimation

- Studied designs

Design (N,n)	Number of patients (N)	Number of doses/patient (n)	Total number of doses	Given doses
(100,7)	100	7	700	1 group (0, 100, 300, 500, 700, 900, 1000)
(100,4)	100	4	400	1 group (0, 100, 300, 1000)
(100,4)*	100	4	400	Optimised
(100,2)*	100	2	200	Optimised
(100,2)	100	2	200	6 groups 1/6 (0, 100) 1/6 (0, 300) 1/6 (0, 1000) 1/6 (100, 300) 1/6 (100, 1000) 1/6 (300, 1000)
(200,2)	200	2	400	

Table 1: Various studied designs

- Prediction of **RSE (D50)** by PFIM 3.2
- **Criterion** of design efficacy = determinant$(M_F)^{1/P}$ P is the total number of population parameters

2. Evaluation of the influence of covariate on D50 on design optimisation and prediction of power of the comparison Wald test for this covariate effect

- Design optimisation for a model without vs. with covariate β_{D50}
  - N = 100 patients
  - Design with 2 doses/patient chosen among (0, 100, 300, 1000)
  - Design with 4 doses/patient chosen among (0, 100, 300, 500, 700, 900, 1000)
- Power of the Wald test for D50 comparison between two treatments A and B
  - With various designs, given (Table 1) or optimised with covariate β_{D50}
  - Prediction of **power** by PFIM 3.2 from the SE of β_{D50}

RESULTS

1. Influence of design on criterion and precision of D50 estimation

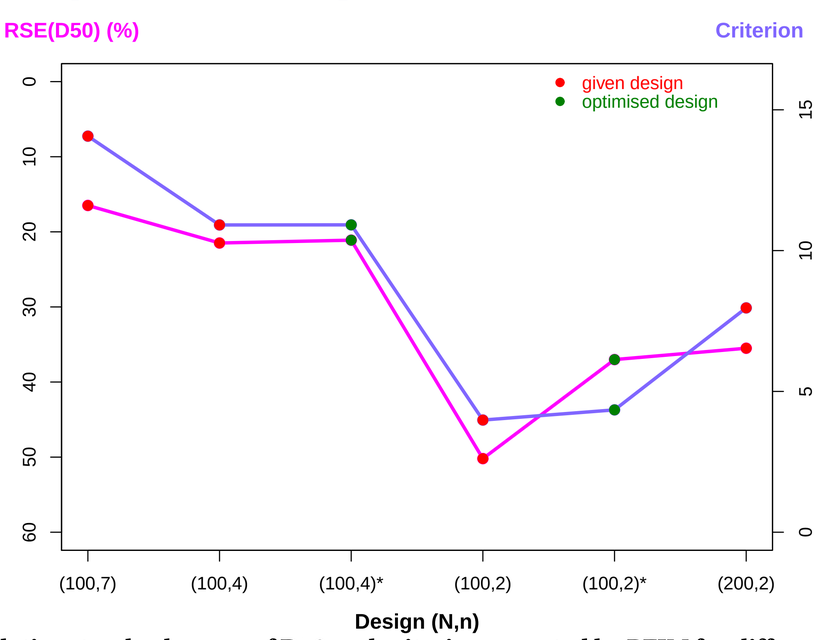

Figure 2: Relative standard errors of D50 and criteria computed by PFIM for different designs

*: optimal design obtained by Fedorov-Wynn algorithm in PFIM for the model without covariate (Table 2)

⇒ **The richer is the design, the larger is the criterion, the more precise is the estimation of D50**

⇒ **Gain on precision with the optimal sparse design vs. the given design with 2 doses**

2. Influence of covariate on D50 on design optimisation and prediction of power of the comparison Wald test for this covariate effect

Optimal design for N = 100	Model without covariate	Model with covariate
n = 2 chosen among (0,100,300,1000)	**3 groups** 3/8 (0, 100) 2/8 (100, 300) 3/8 (300,1000)	**3 groups** 3/8 (0, 100) 2/8 (100, 300) 3/8 (300, 1000)
n = 4 chosen among (0, 100, 300, 500, 700, 900, 1000)	**2 groups** 87/100 (0, 100, 300, 1000) 13/100 (0, 100, 500, 1000)	**1 group** (0, 100, 300, 1000)

Table 2: Optimal designs with 100 patients and 2 or 4 doses/patient obtained with a model with or without covariate on D50

⇒ **Design optimisation for a model without vs. with covariate on D50**
- similar optimal designs with 2 doses/patient
- close optimal designs with 4 doses/patient : very little difference of efficacy criterion between design (100,4) vs. (100,4)* for the model without covariate (< 0.1%)

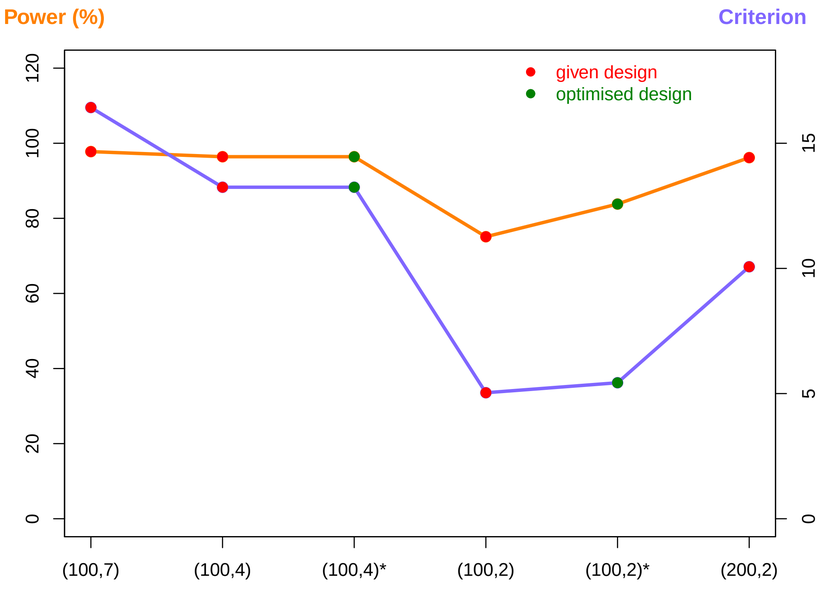

Figure 3: Power of the Wald test for D50 comparison computed by PFIM for different designs and associated criteria

*: optimal design obtained by Fedorov-Wynn algorithm in PFIM for the model with covariate (Table 2)

⇒ **The optimal design (100,2)* provides a power > 80% with twice less samples than design (100,4)**
⇒ **Not much difference in term of power between design (100,7) vs. (100,4)**
⇒ **Difference in term of power between design (100,2) vs. (200,2)**
⇒ **Important impact of the number of subjects on power of tests**

CONCLUSION

- Dose-response studies with several doses/patient can be analysed by NLMEM
- Designs of these studies can be evaluated/optimised using PFIM 3.2: useful tool for designing clinical trials, allowing users to
  - take into account discrete covariates
  - compute power and number of subjects needed

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[4] Bazzoli, C., Retout, S., Mentré, F. (2009) Fisher information matrix for nonlinear mixed effects multiple response models: Evaluation of the appropriateness of the first order linearization using a pharmacokinetic/pharmacodynamic model, *Statistics in Medicine*, 28, 1940-1956
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