DESIGN EVALUATION AND OPTIMISATION IN CROSSOVER PHARMACOKINETIC STUDIES ANALYSED BY NONLINEAR MIXED EFFECTS MODELS

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Outline

Background

- **Crossover pharmacokinetic (PK) trials**
  - Bioequivalence or interaction trials
- **Approaches for analysis of these studies**
  - Non compartmental : >10 samples/subject ⇒ trial in healthy volunteers
  - Nonlinear mixed effects models (NLMEM) : few samples/subject ⇒ trial in patients
- **Importance of choice of design in NLMEM**
  - Balance between number of subjects and number of measures/subject, choice of sampling times
  - Impact on the study results (precision of parameter estimates, power of test)
- **Design evaluation et optimisation**
  - Simulations : cumbersome method
  - Population Fisher information matrix (M_F)
    - Calculation of M_F for NLMEM [1,2] : implementation in PFIM [3,4,5]
    - Not applicable for crossover trials

[1] Mentré et al. *Biometrika*, 1997.
[2] Bazzoli et al. *Stat Med*, 2009.
[3] Retout et al. *Comput Methods Programs Biomed*, 2001.
[4] Bazzoli et al. *Comput Methods Programs Biomed*, 2010.
[5] www.pfim.biostat.fr.

Objectives

- To extend M_F for NLMEM with inclusion of within subject variability (WSV) in addition to between subject variability (BSV) and discrete covariates changing between periods
- To compute the expected power for the Wald test of comparison or equivalence and the number of subjects needed (NSN) for a given power
- To implement these extensions in PFIM 3.2
- To evaluate the relevance of these extensions by simulation
- To apply these extensions to design a future crossover study showing the absence of interaction of a compound X on the PK of amoxicillin in piglets

Notations

N subjects $i = 1, ..., N$
H periods $h = 1, ..., H$

C : set of discrete covariates c
K_c : set of categories k of c

- **Design**
  - ξ_{ih} = vector of n_{ih} sampling times for subject i at period h
  - $\xi_i = (\xi_{i1}, ..., \xi_{ih}, ..., \xi_{iH})$ = elementary design of subject i
  - $\Xi = \{\xi_1, ..., \xi_i, ..., \xi_N\}$ = population design
- **NLMEM**

  Vector of observations of subject i at period h : $y_{ih} = f(\phi_{ih}, \xi_{ih}) + \epsilon_{ih}$

  c_{ih} = covariate c of subject i at period h

  - ϵ_{ih} = residual error $\sim \mathcal{N}(0, \Sigma_{ih})$; $\Sigma_{ih} = \text{diag}(\sigma_{inter} + \sigma_{slope} f(\phi_{ih}, \xi_{ih}))^2$
  - $\phi_{ih} = \mu \exp(\sum_{c \in C} \sum_{k \in K_c} \beta_{c_k} \mathbf{1}_{c_{ih}=k} + b_i + \kappa_{ih})$

    $\left.\begin{array}{l}\mu = \text{fixed effect for the reference category} \\ \beta_{c_k} = \text{fixed effect for the category } k \text{ of } c \text{ (=0 if } k\text{=reference)}\end{array}\right\} \rightarrow \theta$

    $\left.\begin{array}{l}b_i = \text{random effect for subject } i \sim \mathcal{N}(0, \Omega) \\ \kappa_{ih} = \text{random effect for subject } i \text{ at period } h \sim \mathcal{N}(0, \Gamma)\end{array}\right\} \rightarrow v_i$
  - y_i = vector of observations of subject i for all H periods
  - $\Psi = (\theta', \lambda')'$: fixed effects, variances of random effects and of residual errors

Extension of M_F

- Elementary M_F for subject i with elementary design ξ_i :

$$M_F(\Psi, \xi_i) = \mathbb{E}\left(\frac{-\partial^2 l(\Psi, y_i)}{\partial\Psi\partial\Psi'}\right)$$

- Log-likelihood (l) approximation using first-order Taylor expansion of the structural model around the expectation of the random effects(=0) :

$$y_i \cong f(g(\theta, 0), \xi_i) + \left(\frac{\partial f'(g(\theta, v_i), \xi_i)}{\partial v_i}\right)_{v_i=0} v_i + \epsilon_i$$

- Expression of $M_F(\Psi, \xi_i)$: diagonal block matrix
(assumption : independence between variance of the observations and fixed effects)

$\Rightarrow$ Population Fisher information matrix : $M_F(\Psi, \Xi) = \sum_{i=1}^{N} M_F(\Psi, \xi_i)$

$\Rightarrow$ Prediction of standard errors (SE) of discrete covariates fixed or changing between periods from diagonal terms of M_F^{-1}

Prediction of power using M_F

β : covariate effect

Test of comparison

- Test $H_0 : \{\beta = 0\}$ vs. $H_1 : \{\beta \neq 0\}$
- Computing power under H_1, when $\beta = \beta_1 \neq 0$

  $\beta_1 \xrightarrow{\text{Extension of } M_F}$ Standard error $SE(\beta_1)$ [6]

  $$P_{\text{comp}} = 1 - \Phi\left(z_{1-\alpha/2} - \frac{\beta_1}{SE(\beta_1)}\right) + \Phi\left(-z_{1-\alpha/2} - \frac{\beta_1}{SE(\beta_1)}\right)$$

Test of equivalence

- Test $H_0 : \{\beta \leq -\delta \text{ ou } \beta \geq +\delta\}$ vs. $H_1 : \{-\delta < \beta < +\delta\}$ (in general $\delta = 0.2$)
  $\Leftrightarrow$ Schuirmann's TOST $H_{0,-\delta} : \{\beta \leq -\delta\}$ & $H_{0,+\delta} : \{\beta \geq +\delta\}$ [7]
- Computing power under H_1, when $\beta = \beta_1 \in [-\delta, +\delta]$

  $\beta_1 \xrightarrow{\text{Extension of } M_F}$ Standard error $SE(\beta_1)$

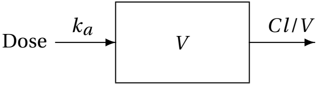
  $$P_{\text{equi}} = 1 - \Phi\left(z_{1-\alpha} - \frac{\beta_1 + \delta}{\text{SE}(\beta_1)}\right) \text{ if } \beta_1 \in [-\delta, 0]\,;\; P_{\text{equi}} = \Phi\left(-z_{1-\alpha} - \frac{\beta_1 - \delta}{\text{SE}(\beta_1)}\right) \text{ if } \beta_1 \in [0, +\delta]$$

NB : Φ = cumulative distribution function of $\mathcal{N}(0,1)$ and z_q such as $\Phi(z_q) = q$

[6] Retout et al. *Stat Med*, 2007.
[7] Schuirmann. *J Pharmacokinet Biopharm*, 1987.

Simulation example

- PK model



PK parameters
$\phi = (k_a, V, Cl)$

- Crossover trials with 2 periods, 1 sequence
  - Period 1 = treatment 1 = A + placebo
  - Period 2 = treatment 2 = A + B
- Treatment effect on Cl : β_{Cl} (interaction of B on A)
- Simulations of 1000 trials with two designs and different values of β_{Cl}

Design	n	N	β_{Cl}
rich (0.5,1,1.5,2,4,6,8h)	7	40	-0.2, 0, 0.1, 0.18, 0.2, 0.4
sparse* (0.5,2,6,8h)	4	40	-0.2, 0, 0.1, 0.18, 0.2, 0.4

* obtained by optimising the rich design of period 1

Evaluation

- For 1000 data sets simulated with each design
  - Estimation of parameters by SAEM algorithm [8,9] in MONOLIX 2.4 [10]
  - Empirical standard error SE_{emp} = sample estimate of the standard deviation from parameter estimates
  - Observed power = proportion of simulated trials for which H_0 is rejected
- By extension of M_F
  - Predicted standard error SE_{M_F}
  - Predicted power from SE of treatment effect parameter

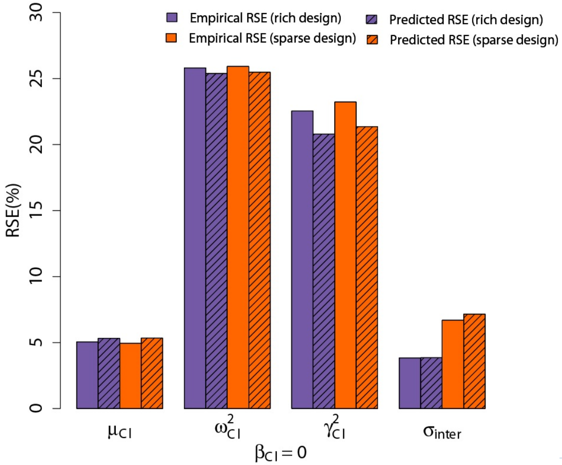
$\Rightarrow$ ***Comparison : simulations vs. predictions***

[8] Kuhn and Lavielle. *Comput Stat Data Anal* 2005.
[9] Panhard and Samson. *Biostatistics* 2009.
[10] www.monolix.org

Results

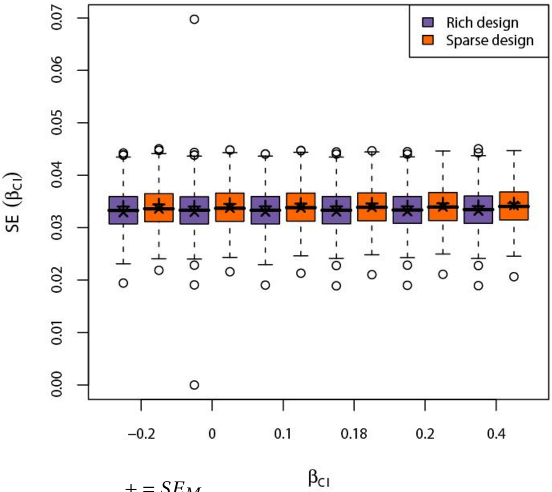
Standard errors

- Relative standard errors (RSE) of parameters



Results

- Boxplots of 1000 $SE(\beta_{Cl})$ of each simulated scenario

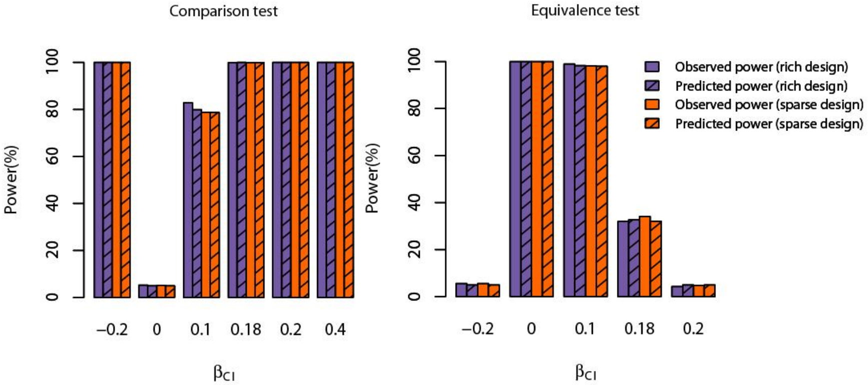


$\times = SE_{emp}$ $+ = SE_{M_F}$

Results

Power of the Wald tests of comparison and equivalence

($\alpha = 0.05$ et $\delta = 0.2$)

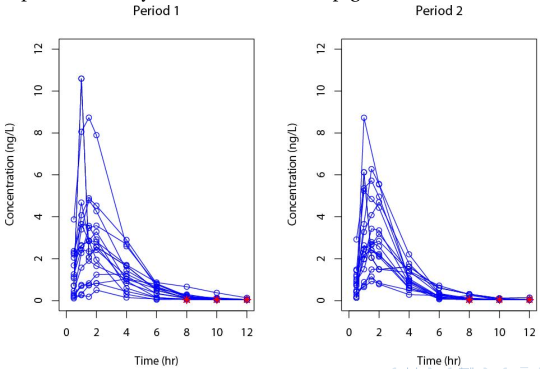


⇒ ***Correct predictions by the extension of M_F for SE as well as for test power***

⇒ ***Similar results between rich design and optimal sparse design***

Application

- Designing a future study DAV2 [11] on the influence of compound X on the PK of amoxicillin in piglets
  - DAV2 similar design as the simulation study : A = amoxicillin, B = compound X
  - Objective of DAV2 : to show the absence of interaction of X on the clearance Cl of amoxicillin
- Analysis of the previous study DAV1 (crossover, 16 piglets)



[11] www.davolterra.com

Application

- Application of the extension of M_F implemented in PFIM
  - Power of the equivalence test for $N = 16$ piglets
  - Number of subjects needed (NSN) for a given power = 90% with an equivalence limit $\delta = 0.2$

Design	β_{Cl}	Power(%)	NSN
Rich (0.5,1,1.5,2,4,6,8,10,12)	0	41.0	68
Sparse (0.5,2,4,6)	0	40.5	70

$\Rightarrow$ ***More piglets to show the absence of interaction of X on the amoxicillin PK in DAV2 with a good power (important within subject variability for Cl = 45%)***

$\Rightarrow$ ***Similar results between rich design and optimal sparse design***

Conclusion

Summary

- Relevance of the extension of M_F in NLMEM for crossover trials : correct predictions of standard errors and powers of tests
- Implementation in PFIM 3.2 (several periods, same elementary design at each period) *January 2010, Copyright © PFIM 3.2 - Caroline Bazzoli, Thu Thuy Nguyen, Anne Dubois, Sylvie Retout, Emmanuelle Comets, France Mentré - Université Paris Diderot-INSERM*

Output PFIM 3.2

```
PFIM 3.2 Option 1
Project:  EVALUATION EXAMPLE
Date:  Fri Apr 02 13:34:05 2010

****************** INPUT SUMMARY *******************
Analytical function models :
dose/V * ka/(ka - (Cl/V)) * (exp(-(Cl/V) * t)
 - exp(-ka * t))

Population design:
Sample times for response: A
                       times subjects doses
1 c(0.5, 1, 1.5, 2, 4, 6, 8)       40    30

Number of occasions: 2
Random effect model: Trand =  2
Variance error model response A : ( 0.1 + 0 *f)^2
Covariate model :
NB: Covariates are additive on log parameters
Covariates changing with occasion
Covariate  1 : Treat ( Cl )
    Categories References
(1)         AP          *
(2)         AX
    Sequences Proportions
(1)     AP AX           1

Computation of the Fisher information matrix:
option =  1

******* POPULATION FISHER INFORMATION MATRIX *******
...

************* EXPECTED STANDARD ERRORS **************
-------------- Fixed Effects Parameters ------------
                      Beta   StdError       RSE
ka                 1.00000000 0.05478405  5.478405 %
V                  3.50000000 0.18646491  5.327569 %
Cl                 2.00000000 0.10643772  5.321886 %
beta_Cl_Treat_AX 0.09531018 0.03405449 35.730174 %

------------- Variance of Inter-Subject Random Effects --------
   Omega   StdError      RSE
ka  0.09 0.02687382 29.85980 %
V   0.09 0.02526824 28.07583 %
Cl  0.09 0.02285511 25.39457 %

------------ Variance of Inter-Occasion Random Effects --------
    Gamma    StdError     RSE
ka 0.0225 0.007998848 35.55044 %
V  0.0225 0.006417971 28.52431 %
Cl 0.0225 0.004679558 20.79804 %

------------ Standard deviation of residual error --------------
           Sigma    StdError     RSE
sig.interA   0.1 0.003837657 3.837657 %

************** DETERMINANT **************
4.596963e+36

************* CRITERION *************
2152.543

***************************** COMPARISON TEST *********************
                      Beta       95 % CI    exp(Beta)       95 % CI
beta_Cl_Treat_AX   0.09531018 [0.029;0.162]       1.1 [1.029;1.176]
Type I error = 0.05
                Expected_power Number_subjects_needed
                                (for a given power=0.9)
beta_Cl_Treat_AX      0.799208              53.65701

***************************** EQUIVALENCE TEST *******************
                      Beta       90 % CI    exp(Beta)      90 % CI
beta_Cl_Treat_AX   0.09531018 [0.039;0.151]       1.1 [1.04;1.163]
Type I error = 0.05
Equivalence interval = [log(0.8),log(1.25)]
                Expected_power Number_subjects_needed
                                (for a given power=0.9)
beta_Cl_Treat_AX      0.982525              24.31024

Time difference of 0.05999994 secs
```

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```

Trial with 2 periods

Covariate model

- AP = amoxicillin+placebo
- AX = amoxicillin+X

SE & RSE of the treatment effect covariate (co-administration of amoxicillin with X) on Cl

Output PFIM 3.2

SE and RSE of the within subject variabilities

90% confidence interval of the covariate effect

Expected power and number of subjects needed for the equivalence Wald test

```
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- Studies analysed through NLMEM can be performed with optimal sparse sampling designs
  - requiring the knowledge of the model and its parameters
  - allowing to reduce the number of samples per subject

$\Rightarrow$ ***Usefulness of PFIM as an efficient tool for design of bioequivalence/ interaction studies analysed by modelling, avoiding extensive simulations***

Perspectives

- Computation of M_F without linearisation of model
- Different optimisation algorithms