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

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BACKGROUND

- **Crossover pharmacokinetic (PK) trials**
  - Bioequivalence or interaction trials
- **Approaches for analysis of these studies**
  - Non compartmental: many samples per subject (>10) ⇒ trial in healthy volunteers
  - Nonlinear mixed effects models (NLMEM): few samples per suject ⇒ 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

OBJECTIVES

1) 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
2) To compute the expected power for the Wald test of comparison or equivalence and the number of subjects needed (NSN) for a given power using the extension of M_F
3) To implement these extensions in PFIM 3.2
4) To evaluate the relevance of these extensions by simulation
5) 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

EXTENSION OF POPULATION FISHER INFORMATION MATRIX

- **Notations**

N subjects $i = 1,...,N$ — C : set of discrete covariates c
H periods $h = 1,...,H$ — 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 $\sim \mathcal{N}(0,\Sigma_{ih})$; $\Sigma_{ih} = \text{diag}(\sigma_{inter} + \sigma_{slope} f(\phi_{ih},\xi_{ih}))^2$
  - $\phi_{ih} = \mu \exp(\sum_{c\in C}\sum_{k\in K_c}\beta_{c_k}\mathbf{1}_{c_{ih}=k} + b_i + \kappa_{ih})$
    μ = fixed effect for the reference category
    β_{c_k} = fixed effect for the category k of c (=0 if k=reference) } → θ = vector of all fixed effects
    b_i = random effect for subject $i \sim \mathcal{N}(0,\Omega)$
    κ_{ih} = random effect for subject i at period $h \sim \mathcal{N}(0,\Gamma)$ } → υ_i = vector of all random effects
  - y_i = vecteur 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)

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

  - Expression of $M_F(\Psi,\xi_i)$: diagonal block matrix

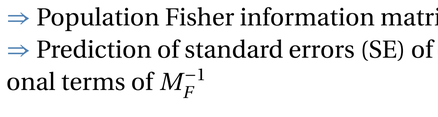
⇒ Population Fisher information matrix : $M_F(\Psi,\Xi) = \sum_{i=1}^{N} M_F(\Psi,\xi_i)$
⇒ Prediction of standard errors (SE) of discrete covariates fixed or changing between periods from diagonal terms of M_F^{-1}

- **Computation of expected 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 $\beta = \beta_1 \neq 0$
      · $\beta_1 \overset{\text{Extension of } M_F}{\longrightarrow}$ Standard error $SE(\beta_1)$ [6]
      · $P_{diff} = 1 - \Phi\left(z_{1-\alpha/2} - \frac{\beta_1}{SE(\beta_1)}\right) + \Phi\left(-z_{1-\alpha/2} - \frac{\beta_1}{SE(\beta_1)}\right)$
  - **Test of equivalence**
    - Test $H_0 : \{\beta \leq -\delta \text{ ou } \beta \geq +\delta\}$ vs. $H_1 : \{-\delta < \beta < +\delta\}$ (in general $\delta = 0.2$)
      ⇔ Schuirmann's TOST $H_{0,-\delta} : \{\beta \leq -\delta\}$ & $H_{0,+\delta} : \{\beta \geq +\delta\}$ [7]
    - Computing power under H_1, when $\beta = \beta_1 \in [-\delta,+\delta]$
      · $\beta_1 \overset{\text{Extension of } M_F}{\longrightarrow}$ Standard error $SE(\beta_1)$
      · $P_{\text{equi}} = 1 - \Phi\left(z_{1-\alpha} - \frac{\beta_1+\delta}{\text{SE}(\beta_1)}\right)$ if $\beta_1 \in [-\delta,0]$; $P_{\text{equi}} = \Phi\left(-z_{1-\alpha} - \frac{\beta_1-\delta}{\text{SE}(\beta_1)}\right)$ if $\beta_1 \in [0,+\delta]$

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

EVALUATION BY SIMULATION

- **Pharmacokinetic 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)

- **Simulation**
  – 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

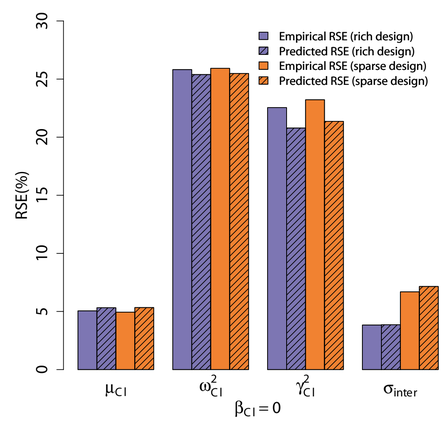
* obtained by optimising the rich design of each period

- **Evaluation method**
  – For 1000 data sets simulated with each design
    - Estimation of parameters by SAEM algorithm [8,9] in MONOLIX 2.4 [10]
    - Empirical SE = 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 SE = SE_{M_F}
    - Predicted power from SE of treatment effect parameter

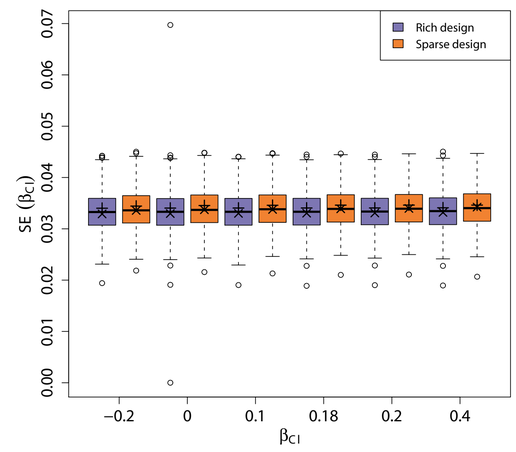
⇒ ***Comparison : simulations vs. predictions***

RESULTS: RELEVANCE OF THE EXTENSION OF M_F

- **Prediction of standard errors**
  – Relative standard errors (RSE) of parameters

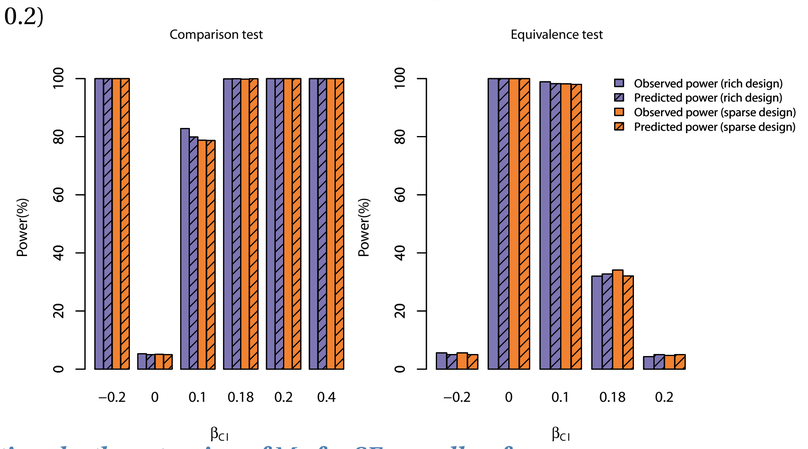


  – Boxplots of 1000 $SE(\beta_{Cl})$ of each scenario



× = SE_{emp} + = SE_{M_F}

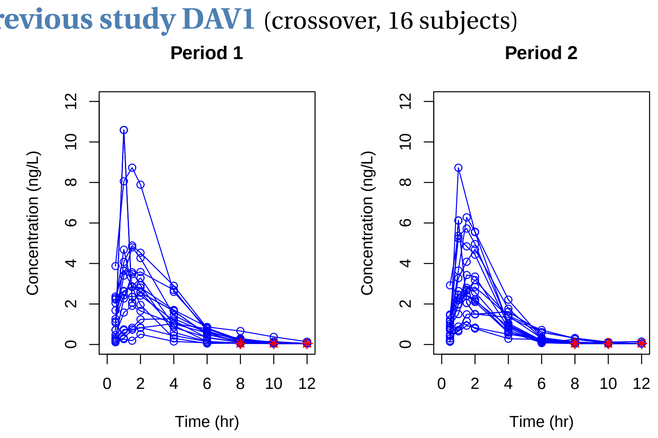
- **Prediction of power for the Wald test of comparison and equivalence**
($\alpha = 0.05$ et $\delta = 0.2$)



⇒ ***Correct predictions by the extension of M_F for SE as well as for power***
⇒ ***Similar results between rich design and reduced design***

APPLICATION

- **Designing a future study DAV2** [11] on the influence of 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 subjects)



- **Application of the extension of M_F implemented in PFIM**
  – Power of the equivalence test for N = 16 subjects
  – 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

⇒ ***Several piglets to show the absence of interaction of X on the amoxicillin PK in DAV2 with a good power***

CONCLUSION

- **Summary**
  – Relevance of the extension of M_F in NLMEM for crossover trials
  – Implementation in PFIM 3.2 (several periods, same elementary design at each period)
  January 2010, Copyright © PFIM 3.2 - C Bazzoli, TT Nguyen, A Dubois, S Retout, E Comets, F Mentré - Université Paris Diderot- INSERM
  – Studies analyzed 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

⇒ ***Usefulness of PFIM as an efficient tool for design of bioequivalence/ interaction studies***

- **Perspectives**
  – Computation of M_F without linearisation of model *(linearisation : potential problems for complex models defined by differential equations)*
  – Different optimisation algorithms

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