EVALUATION OF FISHER INFORMATION MATRIX USING GAUSSIAN QUADRATURE IN NONLINEAR MIXED EFFECTS MODELS
Application to dose-response trials

Thu Thuy Nguyen, France Mentré
University Paris Diderot, Sorbonne Paris Cité, INSERM UMR 738, Paris, France

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

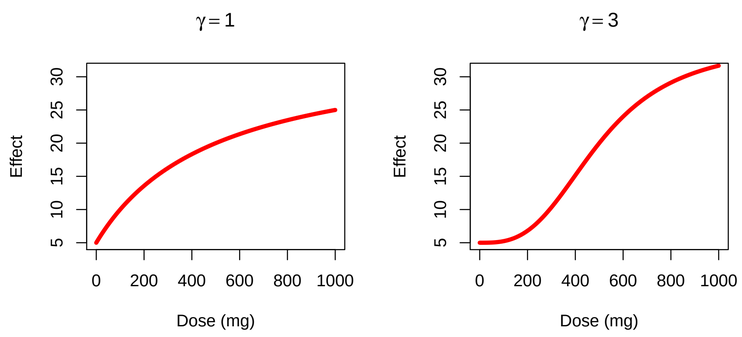
  ⇒ **Modelling through nonlinear mixed effects models (NLMEM)**
- **Importance of choice of design**
  - Trial with one dose/patient: methods to choose robust efficient design for estimating the minimum effective dose already proposed [2]
  - Trial with several doses/patient: how to choose appropriate population design ? (the number of patients ? the number of doses ? which doses ?)

  ⇒ **Increasingly important step: to choose appropriate designs for NLMEM**
- **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
    - Adequacy of the linearisation: influenced by model nonlinearity [7]

  ⇒ **Possible alternative approach: Gaussian quadrature** [8]

MOTIVATING EXAMPLE

- **A dose-response study** [9]
  - **Sigmoid Emax model** $$E = E0 + \frac{Emax \times dose^{\gamma}}{D50^{\gamma} + dose^{\gamma}}$$
  - **Parameters** $E0 = 5$, $Emax = 30$, $D50 = 500$ mg, $\gamma = 1$ or 3
  - **Dose-response curves with $\gamma = 1$ (left) and $\gamma = 3$ (right)**



OBJECTIVES

- **To propose a method to evaluate M_F in NLMEM without linearisation, based on Gaussian quadrature**
- **To evaluate this new method by simulation and compare it to first order approximation for this dose-response sigmoid Emax model with various nonlinearity levels ($\gamma = 1$ or 3)**
- **To illustrate the use of this new method for studying the impact of several designs on D50 precision**

COMPUTING M_F IN NONLINEAR MIXED EFFECTS MODELS

- **Notation**
  - **Design**
    - N patients i
    - n_i doses in patient i
    - $\xi_i = (d_{i1}, ..., d_{ij}, ..., d_{in_i})$ = elementary design in patient i
    - $\Xi = \{\xi_1, ..., \xi_i, ..., \xi_N\}$ = population design
  - **Nonlinear mixed effects model**
    - Individual model $y_i = f(\phi_i, \xi_i) + \epsilon_i$
      - Random error $\epsilon_i \sim \mathcal{N}(0, \Sigma_i)$; $\Sigma_i = \text{diag}(\sigma_{\text{inter}} + \sigma_{\text{slope}} f(\phi_i, \xi_i))^2$
      - Individual parameter ϕ_i
    - Random effect model $\phi_i = g(\mu, b_i) = \mu \exp(b_i)$; $b_i \sim \mathcal{N}(0, \Omega)$, diagonal Ω
    - Population parameter Ψ (size P)
      - Fixed effects μ
      - Variance terms λ = {variances ω^2 of random effects in Ω, σ_{inter} and/or σ_{slope} }
- **Fisher information matrix**
  - Likelihood expressed as an integral $$L(y_i; \Psi) = \int p(y_i|b_i; \Psi) p(b_i; \Psi) db_i$$
  - M_F for elementary design ξ_i $$M_F(\Psi; \xi_i) = \mathbb{E}\left(\frac{-\partial^2 \log L(y_i; \Psi)}{\partial \Psi \partial \Psi'}\right)$$
  - M_F for population design Ξ $$M_F(\Psi; \Xi) = \sum_{i=1}^{N} M_F(\Psi; \xi_i)$$
  - No analytical form for the likelihood L in nonlinear models
- **Computing M_F by linearisation (LIN)**
  - Likelihood approximation using first order expansion of f about random effects taken at 0 [3,4] $$y_i \approx f(g(\mu, 0), \xi_i) + \left(\frac{\partial f'(g(\mu, b_i), \xi_i)}{\partial b_i}\right)_{b_i=0} b_i + \epsilon_i$$
  - Analytical expression for L
  - Mathematical derivations of $L \Rightarrow$ Expression of $M_F(\Psi, \xi_i)$: block diagonal matrix $$M_F(\Psi; \xi_i) = \begin{pmatrix} M_F(\mu; \xi_i) & 0 \\ 0 & M_F(\lambda; \xi_i) \end{pmatrix}$$
  - Implemented in PFIM [6] and several other software
- **Computing M_F by Gaussian quadrature (GQ)**
  - Defining $\eta_i = \Omega^{-1/2} b_i$, then $\eta_i \sim \mathcal{N}(0, I)$, $L(y_i; \Psi) = \int p(y_i|\eta_i; \Psi) p(\eta_i; \Psi) d\eta_i$
  - Integration by quadrature rule, using Gauss-Hermite nodes η_{ik} and weights w_k [10,11] $$L(y_i; \Psi) \approx \sum_{k=1}^{K} w_k p(y_i|\eta_{ik}; \Psi)$$
  - Mathematical derivations of $L \Rightarrow$ Expression of $M_F(\Psi, \xi_i)$ without linearisation $$M_F(\Psi; \xi_i) = \begin{pmatrix} M_F(\mu; \xi_i) & M_F(\mu, \lambda; \xi_i) \\ M_F(\lambda, \mu; \xi_i) & M_F(\lambda; \xi_i) \end{pmatrix}$$
  - Implementation in a working version of PFIM (using function *gauss.quad* of R package *statmod*, 20 nodes)

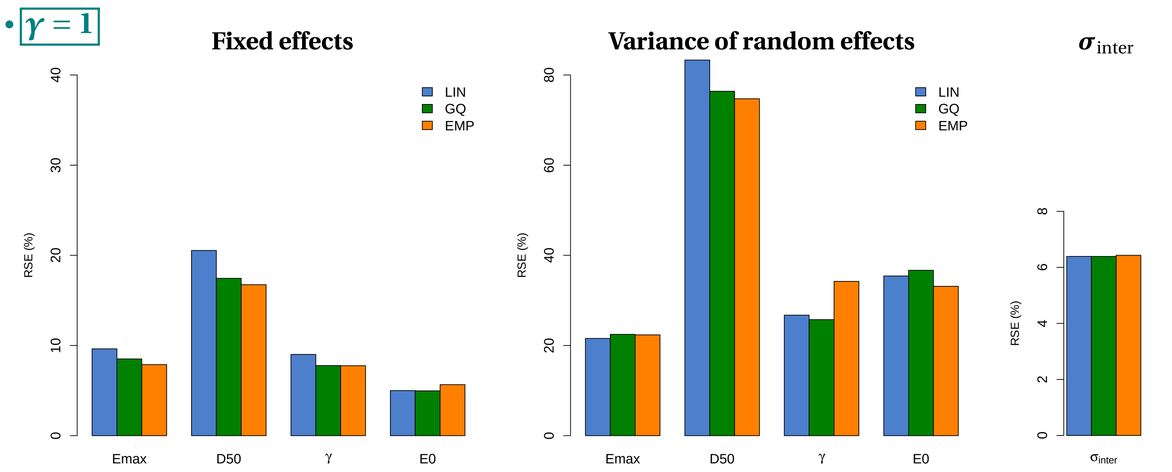
EVALUATION BY SIMULATION

- **Simulation example**
  - **Dose-response trial with several doses/patient**
    - Sigmoid Emax model
    - $\omega = 0.3$ for all parameters
    - $\sigma_{\text{inter}} = 2$, $\sigma_{\text{slope}} = 0$
  - **Design**
    - $N = 100$
    - $n = 4$ doses/patient (0, 100, 300, 1000)
  - **Two simulation scenarii**
    1000 trials of 100 patients
    - $\gamma = 1$ or $\gamma = 3$
- **Evaluation method**
  Comparison of relative standard errors (RSE) between different approaches for each scenario
  - **Predicted RSE from M_F by linearisation in PFIM: RSE_LIN**
  - **Predicted RSE from M_F by Gaussian quadrature: RSE_GQ**
  - **Empirical RSE from repeated simulations: RSE_EMP**
    On 1000 datasets of 100 subjects:
    - Estimation of parameters by SAEM algorithm [12] in MONOLIX 3.2 [13]
    - Empirical standard error = sample estimate of the standard deviation from parameter estimates ⇒ RSE_EMP

  ⇒ **RSE_LIN vs. RSE_GQ vs. RSE_EMP**

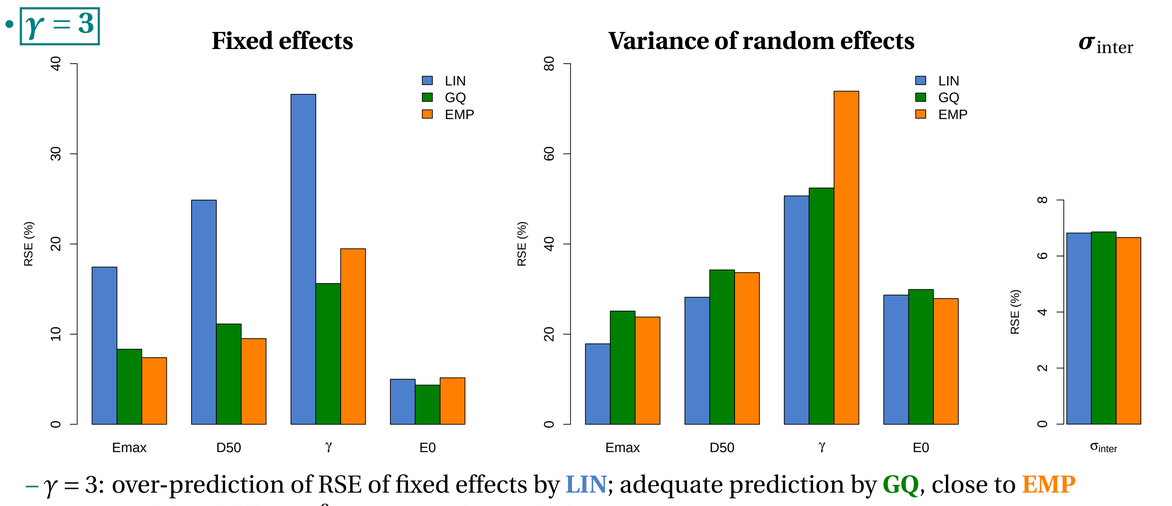
RESULTS

- **$\gamma = 1$**



  - $\gamma = 1$: adequate prediction of RSE by **LIN** and **GQ**, close to **EMP**

- **$\gamma = 3$**



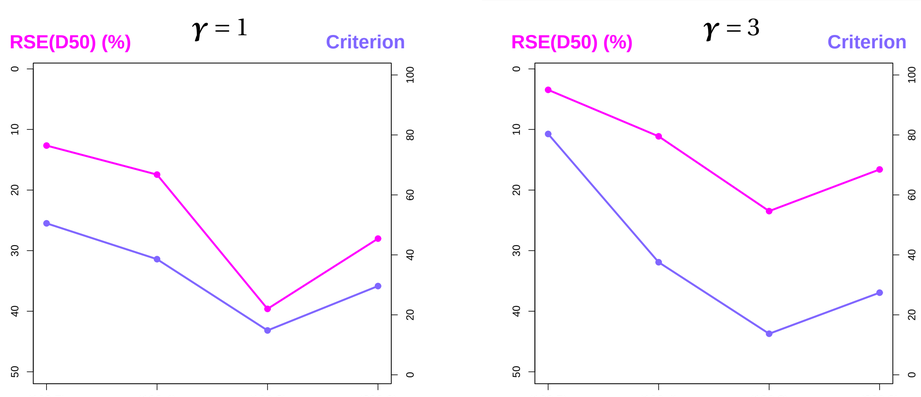
  - $\gamma = 3$: over-prediction of RSE of fixed effects by **LIN**; adequate prediction by **GQ**, close to **EMP**
    large empirical RSE for ω^2_γ > asymptotic predictions

ILLUSTRATION FOR DOSE-RESPONSE TRIAL

- **Objective**
  To illustrate the use of the new method based on Gaussian quadrature for studying the impact of several designs on D50 precision
- **Comparison between 4 designs for $\gamma = 1$ and $\gamma = 3$**
  - **Predicted RSE (D50) (%)**
  - **Criterion = $\det(M_F)^{1/P}$**

  from M_F computed by Gaussian quadrature
- **Results**
- **Studied designs**

N	n	n_{tot}	Doses
100	7	700	(0, 100, 300, 500, 700, 900, 1000)
100	4	400	(0, 100, 300, 1000)
100	2	200	1/6 (0, 100) 1/6 (0, 300) 1/6 (0, 1000)
200	2	400	1/6 (100, 300) 1/6 (100, 1000) 1/6 (300, 1000)



  - The richer is the design, the larger is the criterion, the more precise is the estimation of D50
  - The design (100,4) is better than the design (200,2); RSE(D50) when $\gamma = 3$ < RSE(D50) when $\gamma = 1$

DISCUSSION

- **Summary**
  - Approaches to compute M_F for designing in NLMEM
    - Linearisation approach:
      - moderate nonlinearity level: ok
      - high nonlinearity level: problem
    - New alternative approach based on Gaussian quadrature: avoiding linearisation, giving adequate prediction of SE
  - Dose-response trials with several doses/patient analysed through NLMEM can be designed using Gaussian quadrature
    - Requiring the knowledge of the model and its parameters
    - Complementary approaches: robust approach, sensitivity analysis, adaptive design
- **Prospects**
  - Further evaluation of the new approach with more complex models + link to optimisation
  - Implementation in a future version of PFIM ⇒ useful tool to design dose-response trials

[1] Bretz et al. *Biometrics*, 2005.
[2] Dette et al. *J Am Stat Assoc*, 2008.
[3] Mentré et al. *Biometrika*, 1997.
[4] Bazzoli et al. *Stat Med*, 2009.
[5] Bazzoli et al. *Comput Methods Programs Biomed*, 2010.
[6] www.pfim.biostat.fr.
[7] Han and Chaloner. *Determination & Stochastic Models of AIDS Epidemics & HIV Infections with Intervention*, 2005
[8] Guedj et al. *Bull Math Biol*, 2007.
[9] Plan et al. PAGE, 2010
[10] Golub and Welsch. *Mathematical Computing*, 1969.
[11] Press. *Numerical Recipes in C*, 1992.
[12] Kuhn and Lavielle. *Comput Stat Data Anal* 2005.
[13] www.monolix.org