Designs in nonlinear mixed effects models: evaluation and optimisation of the power of the Wald test with application to HIV viral load decrease.

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Introduction
Population designs : Previous Work (1)

- **Development of the expression of the population Fisher information matrix (M_F) using approximation**
  - First order expansion of the model around the fixed effects

(Mentré, Mallet & Baccar. *Biometrika*, 1997)

- **Extension to the inclusion of the parameter for the variance error model in M_F**
  - σ^2 for homoscedastic or heteroscedastic variance error model

- **First evaluation by simulation of the expected standard errors (SE) of M_F using NONMEM**
  - Relevance of the expected SE compared to the empirical SE computed from the estimated values

(Retout, Bruno & Mentré, *Statistic in Medicine*, 2001)

Introduction
Population designs : Previous Work (2)

- **Implementation of M_F in PFIM 1.0**
  - Splus function for population design evaluation

(Retout, Dufful & Mentré, *Computer Methods and Programs in Biomedicine*, 2001)

- **Extension for combined variance error model: PFIM 1.2**
- **Algorithm for optimisation of the D-optimality criterion**
  - Evaluation of the Simplex algorithm for this task
    - Optimisation of the sampling times in some given continuous intervals
  - Implementation in PFIMOPT 1.0
    - Splus and R function for population design optimisation

(Retout & Mentré, *Journal of Pharmacokinetics Pharmacodynamics*, 2003)

- **Extension of M_F for IOV and covariates**
  - Application to the optimisation of a population design for a real example
    - Population pharmacokinetics of Enoxaparin

(Retout & Mentré, *Journal of Biopharmaceutical Statistics*, 2003)

Introduction
Population designs : Previous Work (3)

- **2 population models for Enoxaparin**
  - 1 compartment, first order absorption and elimination
  - Basic model
    - CL, V, KA (fixed effects), w^2_{CL}, w^2_V (variance parameters), σ^2
  - Rich model
    - Same parameters + influence of covariables on CL and IOV

$$Cl_{ik} = (CL + \beta_{WT}\,(WT_i - 82) + \beta_{CLCR}\,(CLCRi - 87.91))\ \exp\,(b_i + k_{ik})$$

Expected SE (%) with MF for the Rich model

	Design	CL	β_{WT}	β_{CLCR}	w^2_{CL}	IOVCL	σ^2	Eff.
Optimal for Basic model	**N=220 0.5, 4 at D1 2.5, 12 at D3**	**2.3**	**23.9**	**17.3**	**25.1**	**39.9**	**8.8**	**1**
Optimal for Rich model	**N=220 0.5, 12 at D1 2.5, 12 at D3**	**2.2**	**22.4**	**16.3**	**15.8**	**16.7**	**10.2**	**1.2**

Objectives

- **To apply and to illustrate theses optimal design methods to the example of a biexponential model of HIV viral load decrease under antiretroviral treatments**
  - To show the relevance of PFIM for the prediction of the SE of the treatment effect
  - To derive the expected power of the Wald test for this effect from the SE of PFIM
  - To show the influence of the design on this power

Model (1)

- **Viral load decreases after initiation of antiretroviral treatment in HIV1-infected patients**
  - can be described by a bi-exponential model

  (Wu, Ding & De Gruttola, *Statistic in Medicine*, 1998)

- **Statistical model for a subject i with time j**
  - $y_{ij} = f(\phi_i, t_j) + \varepsilon_{ij}$
  - $f(\phi_i, t_j) = \log_{10}(P_{1i} \exp(-\lambda_{1i} t_j) + P_{2i} \exp(-\lambda_{2i} t_j))$
  - $\varepsilon_{ij} \sim N(0, \sigma^2)$.
  - ϕ_i vector of log-parameters for subject i
  - $\phi_i = \mu + b_i$ with $b_i \sim N(0, \Omega)$

Model (2)

- **2 groups of treatments : treatment A and treatment B**
  - additional fixed effect β for the antiretroviral treatment on the first rate–constant
  - $\log(\lambda_1)^B = \log(\lambda_1)^A + \beta$

- **Population parameters to be estimated**
  - $\mu = (\ln(P_1), \ln(P_2), \ln(\lambda_1), \ln(\lambda_2), \beta)$
  - $\mathrm{diag}(\Omega) = (\omega_1^2, \omega_2^2, \omega_3^2, \omega_4^2)$
  - σ^2

Predicted standard error of treatment effect: Comparison of several approaches Method (1)

- **Evaluation with PFIM of an empirical design ("Emp")**
  - two groups of 100 patients with same sampling times
    - 1, 3, 7, 14, 28 and 56 weeks after treatment initiation
  - a priori values of the population parameters (Samson, Lavielle & Mentré, PAGE 2004)

$\ln P_1$	$\ln P_2$	$\ln \lambda_1$	$\ln \lambda_2$	ω_1^2	ω_2^2	ω_3^2	ω_4^2	σ^2
12.0	8.0	-0.7	-3.0	0.3 55%	0.3 55%	0.3 55%	0.3 55%	0.004225 15%

  - evaluation under the null hypothesis H_0: $\beta = 0$.

Predicted standard error of treatment effect: Comparison of several approaches Method (2)

- **For all parameters, comparison of the predicted SE of PFIM to**
  - empirical SE
    - simulations of 100 data files
    - fit using either nlme (Splus) or Monolix, the new SAEM algorithm (MATLAB)

    (Kuhn & Lavielle. *Computational Statistics and Data Analysis*, 2005)

  - an estimate of the expected SE
    - computation under asymptotic convergence assumption by Monolix through a simulation of 5000 patients (exact approach)

Predicted standard error of treatment effect: Comparison of several approaches Results

Comparison of the SE (%) either predicted by PFIM and Monolix, or empirically computed from simulations with nlme and Monolix

	PREDICTED		EMPIRICAL	
	PFIM	Monolix	nlme	Monolix
$\ln P_1$	0.34	0.34	0.35	0.35
$\ln P_2$	0.52	0.57	0.56	0.59
$\ln \lambda_1$	7.9	8.1	7.7	7.8
β	**0.079**	**0.078**	**0.085**	**0.086**
$\ln \lambda_2$	1.3	1.3	1.5	1.5
ω_1^2	10.9	10.8	10.7	10.7
ω_2^2	11.5	12.9	12.0	12.3
ω_3^2	10.3	10.4	9.7	9.7
ω_4^2	10.4	10.8	10.0	11.3
σ	3.5	2.8	3.4	3.4

Power of the test for the treatment effect : Method

- **Derivation of the predicted power of theWald test for β from the predicted SE of "Emp"**

  - statistics for Wald test : β/ SE (β)

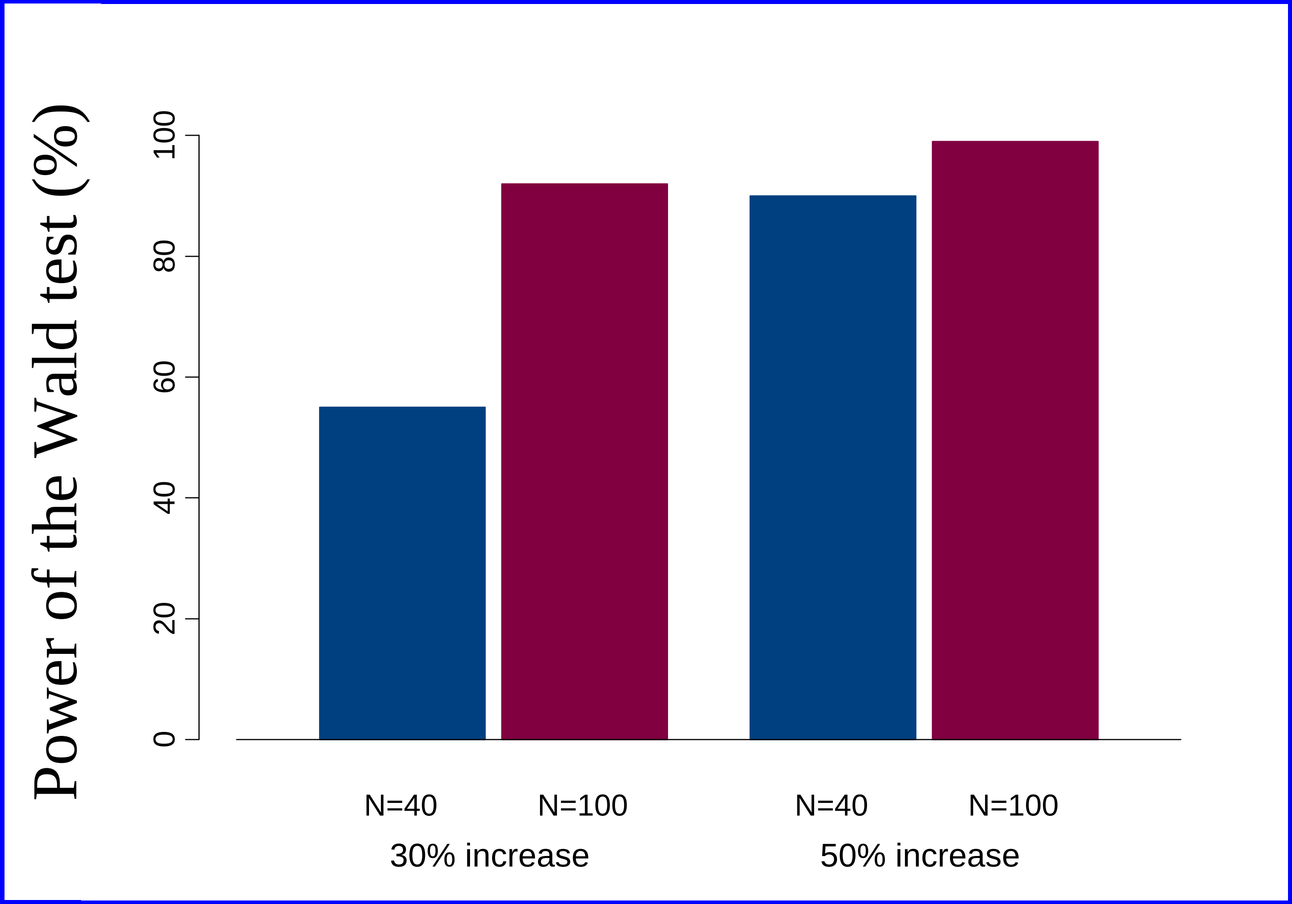
  - require to predict the SE of β under the alternative hypothesis H_1

- **Two different H_1**
  - increase of the first slope by 30% (H_1: $\beta = 0.262$)
  - or increase of the first slope by 50% (H_1: $\beta = 0.405$)

- **Investigation of the influence of the total number of subjects on this power**

Power of the test for the treatment effect : Results

Illustration of the influence of the total number of subjects and of the value of the treatment effect on the power of the Wald test for design Emp.



Designs optimisation using the Fedorov Wynn algorithm: Method (1)

To investigate the influence of the design on the predicted SE and thus predicted power

- **Optimisation of several designs**
  - with either 6, 5, 4 or 3 samples per subject
- **Fedorov-Wynn algorithm**
  - optimisation of both
    - the group structure (number of groups, proportion of subjects per group)
    - the sampling times but in a given finite set of times
      - more clinically relevant compare to the Simplex algorithm
  - convergence toward the D-optimal design

Designs optimisation using the Fedorov Wynn algorithm: Method (2)

- **Set of allowed sampling times**
  - 0, 1, 2, 3, 5, 7, 10, 14, 21, 28, 42 and 56 days

  (Wu & Ding. *Biometrical Journal*, 2002)

- **Constraints**
  - total number of samples fixed to 480
  - same number of subjects with same design in both two groups of treatment (A and B)

- **Optimal numbers of subjects per group derived from the optimised proportions**
  - round to the nearest integer number

Designs optimisation using the Fedorov Wynn algorithm: Results

Optimised designs with several number of samples per subject and influence on the SE of β. Φ_D is the value of the D-optimal criterion for the optimised design.

Design	Number of subjects per group	Number of samples per subject	FW optimisation results {(sampling times), number of subjects}	Φ_D	**SE of β**
Opt6	40	6	$\{(0,1,5,14,21,56),40\}$	471	**0.124**
Opt5	48	5	$\{(0,7,14,21,56),48\}$	523	**0.113**
Opt4	60	4	$\begin{Bmatrix}(0,5,14,56),40\\(0,14,21,56),10\\(0,1,2,3),10\end{Bmatrix}$	536	**0.102**
Opt3	80	3	$\begin{Bmatrix}(7,14,56),35\\(0,1,5),30\\(0,21,56),10\\(0,5,56),5\end{Bmatrix}$	531	**0.095**

Evaluation by simulation of the predicted power: Method

For each optimised design

- Computation of the predicted power of the Wald test for β from its SE given by PFIM
- Simulation of 1000 data sets
  - with R under H1: β = 0.262
- Analyse of the simulated data sets with nlme
- Computation of the empirical power of the test on the 1000 estimated data sets
- Comparison of the empirical power to the predicted power

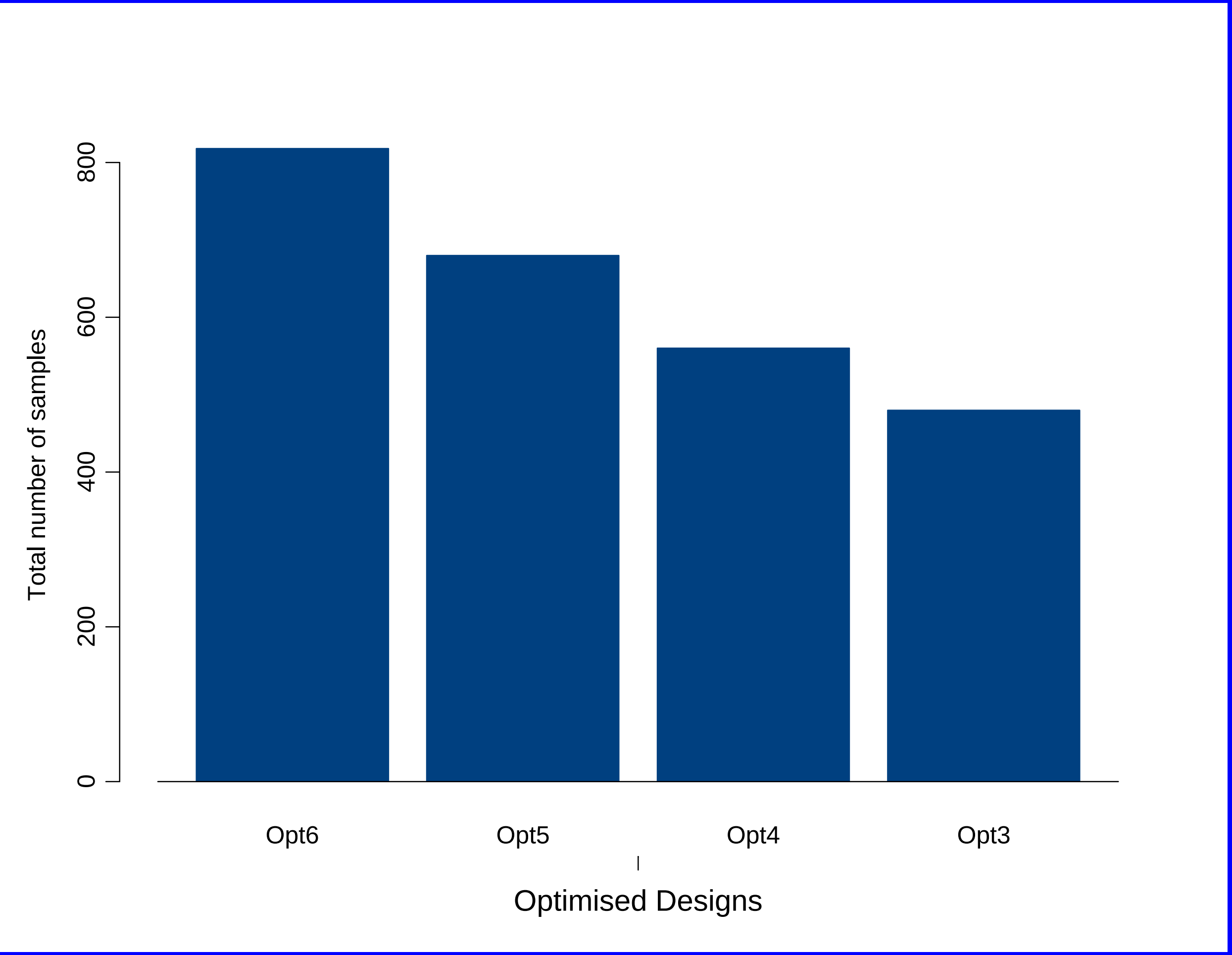
Designs optimisation using the Fedorov Wynn algorithm: Results

Influence of the design on the power of the Wald test and comparison of the power computed from the predicted SE of PFIM to that observed by simulation. Φ_D is the value of the D-optimal criterion for the optimised design

Design	Number of subjects per group	Number of samples per subject	FW optimisation results {(sampling times), number of subjects}	Φ_D	**SE of β**	Computed Power (PFIM)
Opt6	40	6	$\{(0,1,5,14,21,56),40\}$	471	**0.124**	55%
Opt5	48	5	$\{(0,7,14,21,56),48\}$	523	**0.113**	64%
Opt4	60	4	$\left\{\begin{matrix}(0,5,14,56),40\\(0,14,21,56),10\\(0,1,2,3),10\end{matrix}\right\}$	536	**0.102**	73%
Opt3	80	3	$\left\{\begin{matrix}(7,14,56),35\\(0,1,5),30\\(0,21,56),10\\(0,5,56),5\end{matrix}\right\}$	531	**0.095**	79%

Evaluation by simulation of the predicted power: Results

Total number of samples required for optimised designs to achieve a power of 80%. Power is computed from the predicted SE of β of PFIM



Conclusion

Illustration of the great potential of PFIM and PFIMOPT

- **Relevance of the SE computed by PFIM**
  - even on the treatment effect

- **Control and improvement of the power of a Wald test and of the number of patients needed**

- **Interesting and growing field with great potential applications**

Software

- **PFIM 1.2 and PFIMOPT 1.0 in Splus (6 & 2000) and R**
  - www.bichat.inserm.fr/equipes/emi0357/download.html
- **Soon PFIM 2.0 (PAGE 2006)**
  - Library of PK models (in R)
  - ODE (in R)
- **Soon PFIMOPT 2.0 (PAGE 2006)**
  - Library of PK models (in R)
  - ODE (in R)
  - Optimisation with Federov Wynn algorithm
    - for R using C dynamic link library

Perspectives

- **Optimisation with covariates**
  - given distribution
    - optimal designs across patients
    - optimal designs with respect to covariates values
  - optimisation of distribution
    - find best designs and best covariate distribution

- **Optimal design for subset of parameters (D_S-optimality)**
  - ex: to focus on the power of the treatment effect

- **Optimisation with IOV**
  - balance: number of occasions / number of samples per occasion

- **PK/PD and multiresponse models**
  - work in progress with Caroline Bazzoli, Student of Master

back up

Introduction
Population designs : Previous Work (4)

Main Limitations

- **Rely on an approximation of the Fisher information matrix (M_F) using a first order linearization of the model**
  - Validation?
- **Optimisation in PFIMOPT: maximization of the D-optimal**
  - Simplex algorithm: optimisation of the sampling times in some given continuous intervals
    - Can be very cumbersome for large design variables to optimise
  - Fedorov-Wynn algorithm
    - Optimisation of both the group structure and the sampling times but in a given finite set of times
    - Convergence toward the D-optimal design

Evaluation by simulation of the predicted power: Results

Total number of samples required for optimised designs to achieve a power of 80%. Power is computed from the predicted SE of β of PFIM