

Title: An extension of PFIM for optimal population design in multiple response nonlinear mixed effects models: PFIM 3.0

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Background: Models with multiple responses within patients are increasingly used in population analyses, the main example being joint pharmacokinetic (PK) / pharmacodynamic (PD) models. In this context, efficient tools for population designs evaluation and optimisation are necessary. The methodology for optimal population design based on the Fisher information matrix for nonlinear mixed effects models has been initially developed and evaluated [1, 2] for single response models. It has been implemented in several software including PFIM, an R function [3]. Hooker et al. [4] and Gueorguieva et al. [5] have developed the population Fisher information matrix for multiple response models using the same approach than for a single response model.

Objectives: The objectives are to extend PFIM for multiple response models, to improve the specification of the models and the optimisation algorithm and to show results for a PKPD example.

Methods: We developed PFIM 3.0, an extension of PFIM, to accommodate multiple response models. The Fisher information matrix is computed similarly as for single response models using a linearization of the model. We showed the relevance of this approach in a simulation study using a joint PKPD model [6]. Other options have been added in PFIM 3.0 for model specification or optimization. Models can now be specified either with their analytical form or by using a system of differential equations. Moreover a library of analytical pharmacokinetic models has been added. It contains one or two compartment models, after oral administration, bolus or infusion and after a single dose, multiple doses or steady-state. Optimisation of population designs is performed using the D-optimal criterion. For optimization, an alternative to the Simplex algorithm has been implemented in PFIM 3.0, the Federov-Wynn algorithm [7-9]. This algorithm optimizes not only the sampling times, among a given set of possible times, but also the design structure using the approach of statistical designs. In PFIM3.0, it is possible to optimize designs with identical sampling times for all types of responses or different sampling times across responses.

Results: We illustrate the different options of this new extension of PFIM using a real example. We compare and optimise design for the simultaneous population analysis of the time course of warfarin concentration and its effect on the prothrombin complex activity (PCA) after single dose administration. The PD model is an indirect response model defined by a differential equation. The ‘empirical’ design involves one group of 32 healthy volunteers with 13 sampling times at 0.5, 1, 2, 3, 6, 9, 12, 24, 36, 48, 72, 96, 120 hours for warfarin concentration measurements and 7 sampling times at 24, 36, 48, 72, 96, 120, 144 hours for PCA measurement, i.e. a total of 640 measurements. We use the Federov-Wynn algorithm to optimize a population design with only four sampling times common to both responses in the same number of 32 volunteers, the set of admissible sampling times being those of the empirical design. The optimal design is composed of two groups of respectively 10 and 22 subjects and a total of 256 measurements. With this optimal design the expected relative standard errors of estimation are in the same range than those obtained with the empirical design which has 2.5 more measurements.

Conclusions: Population approaches have a rapid development in drug development and new estimation methods have been proposed recently. It is however important beforehand to design informative studies. The use of optimal design in population analysis is spreading. There are different software tools that implement an evaluation of the Fisher information matrix for population PKPD models and propose optimization of population designs [10]. In this framework, PFIM 3.0 is a new and freely available tool in R that can handle models with multiple responses [11].

References:

- [1] Mentré F, Mallet A, Baccar D. Optimal design in random effect regression models. *Biometrika*. 1997; **84(2)**:429-442.
- [2] Retout S, Mentré F, Bruno R. Fisher information matrix for non-linear mixed effects models: evaluation and application for optimal design of enoxaparin population pharmacokinetics. *Statistics in Medicine*. 2002; **21(18)**:2623-39.
- [3] Retout S, Mentré F. Optimization of individual and population designs using Splus. *Journal of Pharmacokinetics and Pharmacodynamics*. 2003; **30(6)**: 417-443.
- [4] Hooker A, Vicini P. Simultaneous population optimal design for pharmacokinetic-pharmacodynamic experiments. *American Association of Pharmaceutical Scientists journal*. 2005; **7(4)**:759-785.
- [5] Gueorguieva I, Aarons L, Ogungbenro K *et al*. Optimal design for multivariate response pharmacokinetic models. *Journal of Pharmacokinetics and Pharmacodynamics* 2006; **33(2)**:97-124.
- [6] Bazzoli C, Retout S, Mentré F. Population Design in Nonlinear Mixed Effects Multiple Response Models: extension of PFIM and evaluation by simulation with NONMEM and MONOLIX. *Group of Population Optimum Design of Experiments*. Sandwich, England, 2007.
- [7] Federov V.V. Theory of optimal experiments. Academic Press: New-York, 1972.
- [8] Wynn H.P. Results in the construction of D-optimum experimental designs. *Journal of the Royal Statistical Society B*. 1972; **34**:133-147.
- [9] Mentré F, Mallet A, Baccar D. Optimal design in random effects regression models. *Biometrika*.1997; **84(2)**: 429-442.
- [10] Mentré F, Duffull S, Gueorguieva I *et al*. Software for optimal design in population pharmacokinetics and pharmacodynamics: a comparison. *Population Approach Group in Europe*. Copenhagen, Denmark, 2007.
- [11] Website: <http://www.pfim.biostat.fr/>