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PFIM 4.0, an extended R program for design evaluation and optimization in nonlinear mixed-effect models

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ABSTRACT

Background and Objective: Nonlinear mixed-effect models (NLMEMs) are increasingly used for the analysis of longitudinal studies during drug development. When designing these studies, the expected Fisher information matrix (FIM) can be used instead of performing time-consuming clinical trial simulations. The function PFIM is the first tool for design evaluation and optimization that has been developed in R. In this article, we present an extended version, PFIM 4.0, which includes several new features.

Methods: Compared with version 3.0, PFIM 4.0 includes a more complete pharmacokinetic/pharmacodynamic library of models and accommodates models including additional random effects for inter-occasion variability as well as discrete covariates. A new input method has been added to specify user-defined models through an R function. Optimization can be performed assuming some fixed parameters or some fixed sampling times. New outputs have been added regarding the FIM such as eigenvalues, conditional numbers, and the option of saving the matrix obtained after evaluation or optimization. Previously obtained results, which are summarized in a FIM, can be taken into account in evaluation or optimization of one-group protocols. This feature enables the use of PFIM for adaptive designs. The Bayesian individual FIM has been implemented, taking into account a priori distribution of random effects. Designs for maximum a posteriori Bayesian estimation of individual parameters can now be evaluated or optimized and the predicted shrinkage is also reported. It is also possible to visualize the graphs of the model and the sensitivity functions without performing evaluation or optimization.

Results: The usefulness of these approaches and the simplicity of use of PFIM 4.0 are illustrated by two examples: (i) an example of designing a population pharmacokinetic study accounting for previous results, which highlights the advantage of adaptive designs; (ii) an example of Bayesian individual design optimization for a pharmacodynamic study, showing that the Bayesian individual FIM can be a useful tool in therapeutic drug monitoring, allowing efficient prediction of estimation precision and shrinkage for individual parameters.

Conclusion: PFIM 4.0 is a useful tool for design evaluation and optimization of longitudinal studies in pharmacometrics and is freely available at http://www.pfim.biostat.fr.

1. Introduction

Nonlinear mixed-effect models (NLMEMs) are frequently used in model-based drug development to analyze longitudinal data [1]. They were initially used in pharmacokinetic (PK) or pharmacodynamic (PD) analyses: PK analysis deals with the time course of drug concentration, whereas PD refers to the relationship between the drug effect and doses or concentrations. The analysis through NLMEMs (i.e. the population approach) allows the estimation of mean parameters, their inter-individual/inter-occasion variability as well as covariate effects, and is appropriate for exploiting the richness of repeated measurements. Consequently, this approach is increasingly used in the biomedical field, not only for PKPD [2,3] or joint PK analysis of parent drugs and their active metabolites [4,5], but also for analyses of viral loads [6], of bacterial resistance to antibiotics [7], and of the dose-response relationship [8]. This approach has become the main statistical tool in pharmacometrics, the science of quantitative pharmacology [9]. To estimate parameters in NLMEMs, maximum likelihood estimation is commonly used, although the likelihood for these models has no analytical solution. Specific algorithms, implemented in several

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software packages, have therefore been proposed to perform this maximization [1,10]. Once population parameters are estimated, individual parameters can be obtained using maximum a posteriori (MAP) Bayesian estimation. This approach optimally incorporates all the information available from the whole population to increase the ability to estimate individual parameters and allows the use of sparse sampling, where few samples are collected from each subject.

Before the estimation step, the investigator of a study is confronted with the choice of the experimental design, which is crucial for efficient estimation of parameters in NLMEMs, especially when the studies are conducted in patients from whom few samples can be taken. A design in NLMEMs, also called a population design, is composed of the number of elementary designs and the specification of each elementary design and the associated number of subjects. In this setting, the term elementary design is used to describe a group of subjects with identical design characteristics. The choice of design consists in determining a balance between the number of subjects and the number of samples per subject, as well as the allocation of informative times and doses, according to experimental constraints. To evaluate and compare designs, the theory of optimum experimental design in classic nonlinear models has been introduced [11–13], based on the expected Fisher information matrix (FIM). The inverse of the FIM, according to the Cramer-Rao inequality, is the lower bound of the variance covariance matrix of any unbiased estimators of the parameters. From the square roots of the diagonal elements of the inverse of the FIM, the predicted standard errors (SE) for estimated parameters can be calculated. A widely used optimality criterion for design optimization is the D-criterion, which consists in maximizing the determinant of the FIM. While the individual FIM for standard nonlinear regression has an analytical expression in fixed effect models, there is no closed form of the population FIM in NLMEMs. That is why linear approximations of the model are common approaches in the design theory to evaluate the population FIM [14–16]. When linearizing the model around a guess value of the fixed effects, the variance of the observations is then independent of the fixed effects, which leads to a block-diagonal expression of the FIM [17]. It has been shown that this simpler expression of the FIM performed better than the full matrix expression given by other linearization approaches, providing results closer to those obtained by clinical trial simulation [18]. This expression of the FIM was extended to design crossover trials, including inter-occasion variability and discrete covariates fixed or changing between periods [19]. Beside the individual and population FIM, the expected Bayesian individual FIM was also developed to predict the estimation error of individual parameters obtained by MAP [20,21]. In addition, the Bayesian FIM can also be used to predict the shrinkage [21], a metric quantifying the informativeness of the individual data and the reliability of individual parameter estimates [22]. The design approach based on these developments using the FIM is a good alternative to clinical trial simulation [23]. However, it requires a priori knowledge of the model and its parameters, which can usually be obtained from previous experiments and which leads to locally optimal designs. Alternatives to locally optimal designs are robust designs, relying on a priori distribution of parameters [24,25], or adaptive designs, which use accumulating information in order to decide how to modify predefined aspects of the study during its implementation instead of leaving them fixed until the end [26,27]. An adaptive design approach in NLMEMs that optimizes the design of each cohort while taking into account previous FIM obtained from previous cohorts has been proposed [28,29].

Expressions of the individual FIM and population FIM based on FO are available in several software tools for designs in NLMEMs [18]. In particular, these expressions were implemented in PFIM, the first R function dedicated to design evaluation and optimization (www.pfim.biostat.fr). PFIM has been available since 2001 [30] for designs in single-response models. Version 3.0 including extensions of PFIM to multiple-response models was released in 2008 and described in [31]. Then version 3.2 was released in 2010, with a more complete PKPD library of models, had additional features, as described in [32], for including inter-occasion variability (IOV), discrete covariates with prediction of power for the comparison or equivalence Wald test [19,33]. PFIM Interface, the graphical user interface (GUI) using R software, is also available and can be used to perform several features of the R script versions of PFIM. Optimization in PFIM is based on the D-optimality criterion described previously. Version 3.0 and later versions implement two optimization algorithms in PFIM: Simplex [34] and the Fedorov-Wynn algorithm [33,35,36].

Several features have been added to the new version 4.0 of PFIM. This new version includes a new input method to specify user-defined models through an R function. Design optimization can now be performed with fixed parameters or fixed sampling times. The FIM obtained after evaluation or optimization can be saved in a file. Evaluation and optimization can also be performed accounting for a previous FIM which summarizes previously obtained results, following the principle of adaptive designs. Additional features based on the Bayesian individual FIM have been implemented. Designs for MAP estimation of individual parameters can be evaluated or optimized and the predicted shrinkage is also reported. Finally, it is now possible to visualize the graphs of the model and the sensitivity functions without necessarily performing evaluation or optimization.

All the new features of PFIM 4.0 are described in this article. Section 2 presents the methodological developments for different new aspects of designs in NLMEMs. Then, the features implemented in PFIM 4.0 and the structure of the R program and its use are presented in Section 3, through a summary of model specifications as well as a description of the input/output files. Lastly, two illustrations of the use of PFIM 4.0 are provided in Section 4: (i) an example of designing a population PK study taking into account previous results and (ii) an example of Bayesian individual design optimization for a dose-response study.

2. Statistical methods

2.1. Design

The elementary design ξ_i of individual i $(i = 1, \ldots, N)$ is defined by the number n_i of samples and their allocation in time $(t_{i1} \ldots, t_{in_i})$. In the case of K responses, ξ_i is composed of K sub-designs such that $\xi_i = (\xi_{i1}, \xi_{i2}, \ldots, \xi_{iK})$. The sub-design ξ_{ik} is then defined by $(t_{ik1}, t_{ik2}, \ldots, t_{ikn_{ik}})$, with n_{ik} sampling times for the observations of the kth response, so that $n_i = \sum_{k=1}^{K} n_{ik}$.

In the case of designs with H occasions, ξ_i is composed of H sub-designs such that $\xi_i = (\xi_{i1}, \xi_{i2}, \ldots, \xi_{iH})$. The design ξ_{ih} at each occasion h $(h = 1, \ldots, H)$ for K responses is composed of $(\xi_{ih1}, \xi_{ih2}, \ldots, \xi_{ihK})$, with $\xi_{ihk} = (t_{ihk1}, t_{ihk2}, \ldots, t_{ihkn_{ihk}})$. The number of sampling times at the h^{th} occasion is $n_{ih} = \sum_{k=1}^{K} n_{ihk}$, so that $n_i = \sum_{h=1}^{H} \sum_{k=1}^{K} n_{ihk}$.

For N individuals, the population design is composed of the N elementary designs such as $\Xi = \{\xi_1, \ldots, \xi_N\}$. Usually, population designs are composed of a limited number Q of groups of individuals with identical design ξ_q within each group, performed in a number N_q of individuals. The population design can thus be written as $\Xi = \{[\xi_1, N_1]; [\xi_2, N_2]; \ldots; [\xi_Q, N_Q]\}$. In the case of identical elementary designs in all individuals, the one-group population design is defined by $\Xi = \{\xi, N\}$.

Individual design (for standard nonlinear regression) and individual Bayesian design (for Bayesian estimation of individual pa-