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Design evaluation and optimisation in multiple response nonlinear mixed effect models: PFIM 3.0

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ABSTRACT

Nonlinear mixed effect models (NLMEM) with multiple responses are increasingly used in pharmacometrics, one of the main examples being the joint analysis of the pharmacokinetics (PK) and pharmacodynamics (PD) of a drug. Efficient tools for design evaluation and optimisation in NLMEM are necessary. The R functions PFIM 1.2 and PFIMOPT 1.0 were proposed for these purposes, but accommodate only single response models. The methodology used is based on the Fisher information matrix, developed using a linearisation of the model. In this paper, we present an extended version, PFIM 3.0, dedicated to both design evaluation and optimisation for multiple response models, using a similar method as for single response models. In addition to handling multiple response models, several features have been integrated into PFIM 3.0 for model specification and optimisation. The extension includes a library of classical analytical pharmacokinetics models and allows the user to describe more complex models using differential equations. Regarding the optimisation algorithm, an alternative to the Simplex algorithm has been implemented, the Fedorov–Wynn algorithm to optimise more practical D-optimal design. Indeed, this algorithm optimises design among a set of sampling times specified by the user. This R function is freely available at http://www.pfim.biostat.fr. The efficiency of this approach and the simplicity of use of PFIM 3.0 are illustrated with a real example of the joint PKPD analysis of warfarin, an oral anticoagulant, with a model defined by ordinary differential equations.

1. Introduction

Nonlinear mixed effect models (NLMEMs) are increasingly used for the analysis of longitudinal data describing a biological process. They allow the estimation of the mean value of parameters in population studies and their inter-individual variability. They are also used for the joint modelling of several biological responses, such as the joint analysis of pharmacokinetic (PK) and pharmacodynamic (PD) data [1]. Pharmacokinetics deals with the time course of drug concentration, whereas pharmacodynamics refers to the time course of drug action in the body. In pharmacometrics, analysis through a NLMEM is called the population approach. To estimate parameters in NLMEMs, maximum likelihood estimation is used primarily, although the likelihood for these models has no analytical solution. Specific algorithms, implemented in several software packages, have therefore been proposed to perform this maximisation [2].

Before the estimation step, the investigator of a study is confronted with the choice of the design which is crucial for an efficient estimation of model parameters. A design in NLMEM, also called a population design, is composed of the number of elementary designs (or groups) and the specifica-

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tion of each elementary design and the associated number of subjects. In this setting, the term elementary design is used to describe a collection of subjects that have identical design characteristics defined by the number of sampling times and their allocation in time. To evaluate and compare population designs, a statistical approach based on the theory of optimum experimental design in classical nonlinear models and described for instance by Atkinson and Donev [3] or by Walter and Pronzato [4] has been extended to NLMEMs. This theory is based on the Fisher information matrix, whose inverse, according to the Cramer–Rao inequality, is the lower bound of the variance covariance matrix of any unbiased estimators of the parameters. Due to the lack of an analytical expression for the likelihood in NLMEM, an exact expression of the Fisher information matrix cannot be defined. That is why an expression based on a linearisation of the model around the expectation of random effects has been proposed by Mentré et al. [5] and extended by Retout and Mentré [6] in the context of a single response model. The usefulness of this approach has been demonstrated, both by simulation [7,8] and in real pharmacokinetic studies [9,10]. To make the procedure more accessible to investigators, the approximate expression of the Fisher information matrix has been implemented in the R function PFIM 1.2, which can be used for design evaluation and comparison [11].

Regarding optimisation, two approaches can be used, either the optimisation of exact designs or of statistical designs. In the case of optimisation of exact designs, the group structure of the design is fixed: the number of elementary designs, the number of samples per design and the number of subjects per elementary design are given and the design variables used to optimise are only the sampling times. Optimisation of statistical designs consists in optimising both the allocation of the sampling times and the whole group structure, that is to say the number of elementary designs, the number of samples per elementary designs and the proportion of subjects in each elementary design. An exact design is then derived by rounding off the proportion of subjects in each elementary design. Optimisation based on the D-optimality criterion has been implemented in the R function PFIMOPT 1.0 [12], where the optimal design is the one that maximises the determinant of the Fisher information matrix. In PFIMOPT 1.0, both exact or statistical optimisation can be performed using the general Simplex algorithm [13]. It optimises the sampling times in given continuous intervals.

The main limitation of PFIM 1.2 and PFIMOPT 1.0 is that both aim at evaluating and optimising population designs only for single response models. Moreover, the model had to be written using an analytic expression and thus the need to use more complex models is limited. Regarding optimisation, the Simplex algorithm is a general optimisation algorithm. However, even if its applicability has been shown in pharmacokinetic examples [8], when there are a large number of parameters to optimise, or when the model is complex, it could have difficulties in converging towards the optimal design and should sometimes be run again using the optimised design as a new initial design.

Recently, the expression for the Fisher information matrix has been extended in the context of a joint estimation of a set of parameters from multiple responses using the same linearisation as for single response [14–16]. In that context, some parameters can be included in several responses, as for instance in a classical PKPD model with the PD response depending on the PK parameters That joined estimation is then more informative, obtaining information on the PK parameters from both PK and PD responses. However, it increases the complexity of the computation of the Fisher information matrix compared to its computation for each response (single response). The relevance of the use of this approximation of the Fisher information matrix for that multiple response NLMEM context has been shown by Bazzoli et al. [14] through simulation of a PKPD model; results were very similar to those obtained from a more exact computation of the information matrix, without any linearisation, using stochastic approximation through the SAEM algorithm of MONOLIX [17].

This expression has been implemented in PFIM 3.0, an extension of PFIM to handle both design evaluation and optimisation in NLMEMs with multiple responses. The extension includes a library of classical analytical pharmacokinetics models and allows more complex models to be described using a system of differential equations. Regarding the optimisation step, an alternative to the Simplex has been added in PFIM 3.0, the Fedorov–Wynn algorithm. It is a specific design optimisation algorithm implemented in PFIM 3.0 for statistical optimisation [5,18] which has the property of converging towards the D-optimal design.

The aim of this paper is to present PFIM 3.0. In section 2, we present a nonlinear mixed effect multiple response design and model and the expression of the population Fisher information matrix for multiple responses. Then, the structure of PFIM 3.0 and the description of its features and use are presented in Section 3. Lastly, an example of the use of PFIM 3.0 to design a new trial for the joint analysis of the pharmacokinetics and pharmacodynamics of warfarin, an oral anticoagulant, is provided in Section 4.

2. Statistical methods

2.1. *Nonlinear mixed effect multiple response design and model*

A design for NLMEM, i.e. a population design, is composed of N individuals to whom we allocate an "elementary" design ξ_i, $i = 1, \ldots, N$. Each elementary design is defined by a number n_i of sampling times and their allocation in time. A population design is therefore described by N elementary designs:

$$\Xi = \{\xi_1, \ldots, \xi_N\} \quad (1)$$

leading to a total number n of observations.

In the case of a multiple response model, an elementary design for one individual i is composed of several sub-designs, i.e. $\xi_i = (\xi_{i1}, \xi_{i2}, \ldots, \xi_{iK})$, where ξ_{ik} is the design associated with the kth response, $k = 1, \ldots, K$. ξ_{ik} is defined by $(t_{ik1}, t_{ik2}, \ldots, t_{ikn_{ik}})$, the vector of the n_{ik} sampling times for the observations of the kth response, so that $n_i = \sum_{k=1}^{K} n_{ik}$.

Usually, population designs are composed of a limited number Q of groups of individuals. Each group is defined by