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Design optimisation in nonlinear mixed effects models using cost functions: application to a joint model of infliximab and methotrexate pharmacokinetics

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Short title: Designs in nonlinear mixed effects models

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Summary

We address the problem of design optimisation using cost functions in nonlinear mixed effects models with multiple responses. We focus on the relative feasibility of the optimised designs, in term of sampling times and of number of subjects. To do that, we extend the Fedorov-Wynn algorithm, a dedicated design optimisation algorithm, to include a cost function that penalizes less feasible designs as well as to take into account multiple responses. We apply this extension to the design optimisation of a joint pharmacokinetic model of infliximab and methotrexate administered in rheumatoid arthritis. We show the benefit of such an approach when substantial constraints on the design are imposed.

Keywords: Design optimisation; nonlinear mixed effects model; cost function; Fedorov-Wynn algorithm; Fisher information matrix, PFIM.

1. Introduction

Nonlinear mixed effects models (NLMEM) are increasingly used in biological studies to analyse longitudinal data. Use of those models has been initiated by Sheiner et al. (1972) for pharmacokinetic (PK) analyses, which study the time course of the drug concentrations in the body after the drug administration. It has been extended for pharmacodynamic (PD) analyses to study the relationship of drug concentrations to pharmacologic effects and it is now very popular in other kinds of longitudinal studies. NLMEM are now also used for the joint modelling of several biological responses such as the PK and the PD of a drug or the PK of parent drugs and of their active metabolite (Panhard et al. (2005)). The purpose of NLMEM approach, also called the population approach, is to estimate the mean value of the parameters and their interindividual variability in the studied population. Influence of covariates on the parameters can also be determined and quantified, which can help to define groups of population with different levels of response. This methodology can deal with sparse individual data, without any need of individual parameter estimates. This allows studies in populations like children for which rich individual data cannot be obtained due to ethical or physiopathological reasons.

As in all experiments, a design has first to be defined to collect the data. Estimation is then performed, usually using maximum likelihood procedures; several estimation methods are available, either based on linearisation of the likelihood function (Beal and Sheiner (1992)) or stochastic approximations (Pinheiro and Bates (1995), Kuhn and Lavielle (2005)). A review of recent advances in this field can be found in Pillai et al. (2005). The choice of the design is important because it largely influences the precision of the parameter estimates. In NLMEM, designs, also called “population designs”, are defined by several groups of subjects; each group is composed of a number of samples to be performed on a number of subjects at given

times. Simulation studies have shown that the precision of parameter estimates depends on the balance between the design variables in the group structure (number of groups to include, number of subjects per group and number of samples per group) and the allocation of the sampling times (Al-Banna et al. (1990); Jonsson et al. (1996)). The general theory of design determination used for classical nonlinear models (Atkinson and Donev (1992); Walter and Pronzato (1997)) has been extended to NLMEM. It relies on the Cramer-Rao inequality which states that the inverse of the Fisher information matrix (M_F) is the lower bound of the variance-covariance matrix of any unbiased maximum likelihood parameter estimator. However exact analytical expression of M_F cannot be derived in NLMEM due to the lack of analytical expression of the likelihood. To circumvent this problem, Mentré et al. (1997) have proposed, for single response models, an approximation of the matrix based on first order Taylor expansion of the model around the expectation of the random effects. This expression has been extended for more complex models including fixed effects for the influence of covariates on the response and for an additional variability of the parameters of a given individual between several periods of treatment (Retout and Mentré (2003a)). Evaluation of M_F using a first order expansion is also performed in Fedorov et al. (2002) and Gagnon and Leonov (2005). Recently, an approximate M_F has been proposed for multiple response models by Hooker and Vicini (2005) and Gueorguieva et al. (2006) using the same first order linearisation of the model. Simulations have shown the approximate M_F to be appropriate for single response models (Retout and Mentré (2003a); Retout et al. (2002); Retout et al. (2007)) and for multiple response models (Bazzoli et al. (2007)); it has been implemented in PFIM, a R function for design evaluation and optimisation freely available online (Retout et al. (2001); Retout and Mentré (2003b); www.pfim.biostat.fr).

Design optimisation can either be restricted to optimising the sampling times for a given group structure (exact designs), or optimise both the group structure and the sampling times

(called statistical or approximate designs) (Atkinson and Donev (1992)). We consider the latter approach in this paper. The Fedorov-Wynn algorithm, a design-specific optimisation algorithm converging towards the D-optimal design (Fedorov (1972); Wynn (1972)), has been implemented for this purpose in PFIM. Its effectiveness to optimise designs in NLMEM, which often involve large number of design variables, has been shown for instance in Retout et al. (2007), by comparison to the Simplex algorithm. The implementation assumes that the acceptable sampling times are given and constitute a finite set for optimisation, which can be a great advantage in clinical practice to avoid unfeasible sampling times.

However, optimisation is performed for a fixed total number of samples without any consideration on the relative feasibility of the sampling times or of the group structure. In practice, however, it may be difficult to keep a patient at the hospital for a long time after its drug administration for no other medical reason than to obtain a blood sample for the study. Recruiting a large number of patients can also be problematic for financial and /or recruitment reasons. This problem has been introduced for single response models through the use of cost functions by Mentré et al. (1997); Gagnon and Leonov (2005) illustrate and highlight the benefits of such an approach on a clinical PK study.

In this work, our objectives are first to extend the Fedorov-Wynn algorithm for design optimisation with cost functions in NLMEM with multiple responses and second, to apply this approach to design optimisation for a joint model of infliximab and methotrexate PK administered in rheumatoid arthritis.

We describe the case study in Section 2. The statistical methods are given in Section 3. We first present NLMEM; we then describe the computation of the Fisher matrix in this context; last, we explain the designs optimisation with cost functions using the Fedorov-Wynn algorithm. Section 3 is dedicated to the application to our case study.

2. Case study: joint model of infliximab and methotrexate

pharmacokinetics

Infliximab is a high-molecular-weight chimeric monoclonal IgG1 antibody against human tumour necrosis factor- α (TNF α). It is given in rheumatoid arthritis to stop the inflammatory process in the synovial joints, in combination with methotrexate, an antimetabolite of folic acid; methotrexate attenuates the formation of antibodies which can inactivate infliximab (Klotz et al. (2007)). To our knowledge, no study has been performed to simultaneously model the population PK of infliximab and methotrexate. However, this modelling is important since many patients receive an association of these two drugs in treatment and because methotrexate has an effect on the PK of infliximab (Klotz et al. (2007)).

2.1. Pharmacokinetics of infliximab

Infliximab is given as a long-term treatment in rheumatoid arthritis since it is a chronic disease. Treatment is usually initiated with 3 infusions at week 0, 2 and 6, and a maintenance dose is given every 8 weeks thereafter. The recommended dose is given as a 2 or 3 hours infusion of 3 mg/kg. The PK of infliximab has been described in patients with rheumatoid arthritis in several papers (Kavanaugh et al. (2000); Klotz et al. (2007); Maini et al. (1998); St Clair et al. (2002)). It is best described by a one compartment model with first order elimination and zero order infusion. It can be parameterized in clearance (Cl) and volume of distribution (V). An exponential model is used to relate individual parameters and random effects, eg for clearance:

$$Cl_i = Cl \exp(b_{i,Cl})$$

where Cl is the mean population value and Cl_i and $b_{i,Cl}$ are respectively the individual clearance parameter and random effect for individual i . The plasma concentration f_{Infl_i} at time t after dose at steady state can be written as follows:

$$f_{Infli}(t) = \begin{cases} \frac{D}{T_{Inf}} \frac{1}{Cl} \left[\left(1 - e^{-\frac{Cl}{V}t} \right) + e^{-\frac{Cl}{V}\tau} \frac{(1 - e^{-\frac{Cl}{V}T_{Inf}}) e^{-\frac{Cl}{V}(t-T_{Inf})}}{1 - e^{-\frac{Cl}{V}\tau}} \right] & \text{if } t \leq T_{Inf} \\ \frac{D}{T_{Inf}} \frac{1}{Cl} \left[\frac{(1 - e^{-\frac{Cl}{V}T_{Inf}}) e^{-\frac{Cl}{V}(t-T_{Inf})}}{1 - e^{-\frac{Cl}{V}\tau}} \right] & \text{if not} \end{cases}$$

where D is the dose, T_{Inf} is the duration of the infusion and τ is the interval between two infusions. Population parameter values are given in Table 1 (Kavanaugh et al. (2000)).

2.2. Pharmacokinetics of methotrexate

The usual dose of methotrexate in rheumatoid arthritis is within a range of 5 – 7.5 mg/week. The PK profile of methotrexate has been described in many papers, including modelling through population approaches. It is best described by a two-compartment first order oral absorption model (Godfrey et al. (1998)). It is parameterized in rate constant of absorption (k_a), clearance (Cl), central compartment volume (V_c), peripheral compartment volume (V_p), intercompartmental clearance (Q), with an exponential modelling of the random effects. To simplify the model, we neglect the oral absorption lag of 0.23h and assume a bioavailability of 100%. Therefore, the plasma concentration f_{Metho} at time t after dose at steady-state can be written:

$$f_{Metho}(t) = D \left(\frac{Ae^{-\alpha t}}{1 - e^{-\alpha\tau}} + \frac{Be^{-\beta t}}{1 - e^{-\beta\tau}} - \frac{(A+B)e^{-k_a t}}{1 - e^{-k_a\tau}} \right)$$

where D is the dose, τ is the interval between two doses, $\alpha = \frac{Q}{\beta} \frac{Cl}{V_p V_c}$,

$$\beta = \frac{1}{2} \left(\frac{Q}{V_c} + \frac{Q}{V_p} + \frac{Cl}{V_c} - \sqrt{\left(\frac{Q}{V_c} + \frac{Q}{V_p} + \frac{Cl}{V_c} \right)^2 - 4 \frac{Q}{V_p V_c}} \right), \quad A = \frac{k_a}{V_c} \frac{Q - \alpha}{(k_a - \alpha)(\beta - \alpha)} \text{ and}$$

$$B = \frac{k_a}{V_c} \frac{\frac{Q}{V_p} - \beta}{(k_a - \beta)(\alpha - \beta)}$$

Population parameter values are given in Table 1 (Godfrey et al. (1998)).

2.3. Design for a joint PK modelling

We aim at determining a design for a joint population analysis of infliximab and methotrexate PK at steady state. The mean kinetic profiles of both drugs are represented on Figure 1, assuming, as we will in the rest of this paper, a 3 hours infusion dose of infliximab of 210 mg every 8 weeks, corresponding to a dose of 3 mg/kg for a mean weight of 70 kg, and a weekly dose of methotrexate of 7.5 mg.

We assume a proportional error model for the infliximab concentrations: $Var(\epsilon) = (0.2 f_{Infli})^2$ and a combined error model for methotrexate: $Var(\epsilon) = (0.01 + 0.2 f_{Metho})^2$.

Our motivation in this paper is to develop optimal designs under different constraints, taking into account different relative feasibilities in clinical practice, such as the inconvenience for patients to be kept a long time at the hospital after its dose administration or the increase of cost induced by the inclusion of a new patient compared to additional samples in a patient already included.

We compare the optimal designs to a design established empirically, by taking into account the very different time scales of the PK course of each drug (Figure 1). This design involves one group of 50 subjects in whom 12 samples are taken. At each sampling time, both infliximab and methotrexate concentrations are measured, yielding a total number of samples of 1200. Six samples are taken on Day 1 of Week 1, after the beginning of the infusion of infliximab at 30 minutes, 1, 3, 6, 8 and 24 hours; the same six samples are repeated at Day 1 of Week 8, the day of the last dose of methotrexate before the next infusion of infliximab. Both periods correspond to a 24 hour period after the administration of a dose of

methotrexate, and should also be informative for infliximab since they are set respectively at the beginning and end of the dosing interval for this drug. We call this design the “empirical design”. The sampling times of this design are reported on the kinetic profiles of infliximab and methotrexate for the mean parameters at steady state on Figure 1.

3. Statistical Methods

3.1. Notations

We define an elementary design as a set of sampling times. A population design is then composed of N individuals each with an associated elementary design ξ_i ($i = 1, \dots, N$). Let n_i denote the number of sampling times in ξ_i . We write the population design $\Xi = \{\xi_1, \dots, \xi_N\}$,

and $n = \sum_{i=1}^N n_i$ the total number of observations.

For multiple response model, an elementary design ξ_i is composed of several sub-designs $\xi_i = (\xi_{i1}, \xi_{i2}, \dots, \xi_{iK})$ with ξ_{ik} , $k = 1, \dots, K$, being the design associated with the k^{th} response.

ξ_{ik} is defined by $(t_{ik1}, t_{ik2}, \dots, t_{ikn_{ik}})$, the vector of the n_{ik} sampling times for the observations of the k^{th} response, so that $n_i = \sum_{k=1}^K n_{ik}$. This notation accounts for different number of samples

and different sampling times across the different responses, to accommodate different response profiles.

Usually, population designs are composed of a limited number Q of groups of different elementary designs ξ_q , $q = 1, \dots, Q$, to be performed in a number N_q of individuals with

$\sum_{q=1}^Q N_q = N$. The population design can then be noted:

$$\Xi = \{[(\xi_{11}, \xi_{12}, \dots, \xi_{1K}), N_1]; [(\xi_{21}, \xi_{22}, \dots, \xi_{2K}), N_2]; \dots; [(\xi_{Q1}, \xi_{Q2}, \dots, \xi_{QK}), N_Q]\}$$

A nonlinear mixed effects multiple response model or a multiple response population model is defined as follows. The vector of observations Y_i for the i^{th} individual is defined as the n_i -vector of the K different responses $Y_i = [y_{i1}^T, y_{i2}^T, \dots, y_{iK}^T]^T$, where y_{ik} , $k = 1, \dots, K$, is the n_{ik} -vector of observations for the k^{th} response. Each of these responses is associated with a known function f_k , such that $f_k(\theta_i, \xi_{ik}) = [f_k(\theta_i, t_{ik1}), f_k(\theta_i, t_{ik2}), \dots, f_k(\theta_i, t_{ikn_k})]^T$ is a n_{ik} -vector which describes the nonlinear model. The K functions f_k can be grouped in a vector of multiple response models F , such as $F(\theta_i, \xi_i) = [f_1(\theta_i, \xi_{i1})^T, f_2(\theta_i, \xi_{i2})^T, \dots, f_K(\theta_i, \xi_{iK})^T]^T$. θ_i denotes the vector of individual parameters in individual i ; some parameters may be shared across different model functions (eg parent/metabolite model or PK/PD model). θ_i is defined by $\theta_i = g(\beta, b_i)$ where β is the vector of the fixed effects parameters, b_i the vector of the random effects for individual i and g , a known function. It is assumed that $b_i \sim N(0, \Omega)$. The function g usually assumes an additive relation between the fixed effect and the random effect of each θ_i , which are thus normally distributed. We consider here a more general g function, which allows us to consider θ_i as the PK parameters, and not as some transformed parameters.

In condensed form, we thus write the statistical model for the nonlinear multiple response mixed-effect model:

$$Y_i = F(g(\beta, b_i), \xi_i) + \varepsilon_i$$

where ε_i is the vector composed of the K vectors of residual errors ε_{ik} , $k = 1, \dots, K$, associated with the K responses. Conditionally on the value of b_i , we assume that the errors ε_i are independently distributed and that $\varepsilon_{ik} \sim N(0, \Sigma_{ik}(\beta, b_i, \sigma_k, \xi_{ik}))$, with σ_k the vector of parameters characterising the k^{th} variance error model. We then note $\Sigma_i = \Sigma_i(\beta, b_i, \sigma, \xi_i)$ the

block diagonal variance matrix of ε_i over the K responses; Σ_i is composed of the elements of Σ_{ik} and σ the vector of the K components σ_k .

Let Ψ be the P -vector of population parameters to be estimated $\Psi^T = (\beta^T, v(\Omega), \sigma^T)$, where $v(\Omega)$ denotes the distinct elements of Ω . We also note λ be the vector of variance terms $\lambda^T = (v(\Omega), \sigma^T)$, so that $\Psi^T = (\beta^T, \lambda^T)$.

3.2. Fisher information matrix for NLME multiple response models

The population Fisher information matrix $M_F(\Psi, \xi)$ for multiple response model for one

individual with design ξ is given by $M_F(\Psi, \xi) = E\left(-\frac{\partial^2 l(\Psi; Y)}{\partial \Psi \partial \Psi^T}\right)$, where $l(\Psi; Y)$ is the log

likelihood of the vector of observations Y of that individual for the population parameters Ψ .

Note that for sake of simplicity, we omit the index i for the individual in this section. Because

F is nonlinear, there is no analytical expression for the log-likelihood $l(\Psi; Y)$. As in Mentré

et al. (1997), a first-order Taylor expansion of the structural model $F(\theta, \xi) = F(g(\beta, b), \xi)$

around the (zero) expectation of b is used:

$$F(g(\beta, b), \xi) \cong F(g(\beta, 0), \xi) + \left(\frac{\partial F^T(g(\beta, 0), \xi)}{\partial b}\right) b$$

Assuming the individual parameters θ are normally distributed, this expansion is equivalent

to the one around β as in Gagnon and Leonov (2005). The statistical model can then be

written as: $Y \cong F(g(\beta, 0), \xi) + \left(\frac{\partial F^T(g(\beta, 0), \xi)}{\partial b}\right) b + \varepsilon$.

For sake of simplicity, we further assume that the variance of the error model does not depend

on the random effects of the individual but only on the mean parameters, so that

$\text{Var}(\varepsilon) = \Sigma(\beta, 0, \sigma, \xi)$. The log-likelihood l is then approximated by:

$$-2l(\Psi; Y) \cong n \ln(2\pi) + \ln(|V|) + (Y - E)^T V^{-1} (Y - E)$$

where E and V are the approximated marginal expectation and variance of Y given by:

$$E(Y) \cong E = F(g(\beta, 0), \xi)$$

$$Var(Y) \cong V = \left(\frac{\partial F^T(g(\beta, 0), \xi)}{\partial b} \right) \Omega \left(\frac{\partial F(g(\beta, 0), \xi)}{\partial b^T} \right) + \Sigma(\beta, 0, \sigma, \xi)$$

Based on this expression of the log-likelihood l , the expression of an elementary Fisher information matrix for multiple response model can be derived. It is a block matrix depending on the approximated marginal expectation E and variance V of the observations:

$$M_F(\Psi, \xi) \cong \frac{1}{2} \begin{pmatrix} A(E, V) & C(E, V) \\ C^T(E, V) & B(E, V) \end{pmatrix}$$

$$\text{where } (A(E, V))_{mn} = 2 \frac{\partial E^T}{\partial \beta_m} V^{-1} \frac{\partial E}{\partial \beta_n} + tr \left(\frac{\partial V}{\partial \beta_n} V^{-1} \frac{\partial V}{\partial \beta_m} V^{-1} \right) \text{ with } m \text{ and } n = 1, \dots, \dim(\beta)$$

$$(B(E, V))_{mn} = tr \left(\frac{\partial V}{\partial \lambda_m} V^{-1} \frac{\partial V}{\partial \lambda_n} V^{-1} \right) \text{ with } m \text{ and } n = 1, \dots, \dim(\lambda)$$

$$(C(E, V))_{mn} = tr \left(\frac{\partial V}{\partial \lambda_n} V^{-1} \frac{\partial V}{\partial \beta_m} V^{-1} \right) \text{ with } n = 1, \dots, \dim(\lambda) \text{ and } m = 1, \dots, \dim(\beta)$$

The population Fisher information matrix for a population design Ξ , is thus derived as the sum of the N elementary Fisher information matrices with ξ_i for each individual i :

$$M_F(\Psi, \Xi) = \sum_{i=1}^N M_F(\Psi, \xi_i). \text{ In the case of a limited number } Q \text{ of groups, this matrix is}$$

$$\text{expressed as } M_F(\Psi, \Xi) = \sum_{q=1}^Q N_q M_F(\Psi, \xi_q).$$

3.3. Fedorov-Wynn algorithm for design optimisation using cost functions

Design optimisation with cost functions

We consider design optimisation within a finite set of possible designs S . The objective is to maximise in some sense the information matrix of the population design, $M_F(\Psi, \Xi)$, since the variance of the estimate is asymptotically proportional to $M_F^{-1}(\Psi, \Xi)$. Here, we use the D-optimality criterion, which consists in maximising $\det(M_F(\Psi^0, \Xi))$, where \det denotes the determinant and Ψ^0 a given a priori value of the population parameters. In the following, we will drop the explicit dependency on Ψ^0 in the notation, and write $M_F(\Xi) = M_F(\Psi^0, \Xi)$ for simplicity. We also consider the normalised information matrix, defined by

$$I_F(\Xi) = \frac{M_F(\Xi)}{N} = \sum_{q=1}^Q \frac{N_q}{N} M_F(\xi_q) \quad (\text{Gagnon and Leonov (2005)}).$$

This matrix represents the average information matrix for one individual in design Ξ .

For a given maximal number of subjects to be included, N , which will be attained for the optimal design, and in the absence of other constraints, the maximisation problem is to find Ξ^* such that:

$$\Xi^* = \arg \max_{\Xi} \det(M_F(\Xi)) = \arg \max_{\Xi} \det\left(N \sum_{q=1}^Q \alpha_q M_F(\xi_q)\right) \quad (1)$$

where Ξ is defined by a set of Q elementary designs and their associated frequencies

$$\left\{ \left(\alpha_q = \frac{N_q}{N}, \xi_q \right), q = 1, \dots, Q \right\}, \text{ where } \xi_1, \dots, \xi_Q \text{ are in } S, \text{ and the frequencies satisfy } 0 \leq \alpha_q \leq 1$$

$$\text{and } \sum_{q=1}^Q \alpha_q = 1.$$

Note that (1) is equivalent with N fixed to solving $\Xi^* = \arg \max_{\Xi} \det(I_F(\Xi))$. Even though the N_q should technically be integers, the problem is usually solved assuming that α_q is

continuous and rounding off the resulting $N_q = N\alpha_q$ under the constraint $\sum_{q=1}^Q N_q = N$. The optimisation problem is therefore a maximisation problem on a convex compact surface given by $\sum_{q=1}^Q \alpha_q = 1$ (Atkinson and Donev (1992)).

We now assume, following Mentré et al. (1997) and Gagnon and Leonov (2005), that there is a cost incurred by each elementary design, which we denote $C(\xi)$. Instead of a maximum number of subjects, we set a maximal cost C_{tot} , such that $N \sum_{q=1}^Q \alpha_q C(\xi_q) \leq C_{tot}$. The optimal population design again satisfies the equality. Introducing C_{tot} and $C(\xi)$, the criterion to be maximised in (1) can be rewritten as:

$$\det(M_F(\Xi)) = \det\left(N \sum_{q=1}^Q \alpha_q M_F(\xi_q)\right) = \det\left(\sum_{q=1}^Q w_q \left(M_F(\xi_q) \frac{C_{tot}}{C(\xi_q)}\right)\right)$$

where $w_q = \frac{N\alpha_q C(\xi_q)}{C_{tot}}$ and corresponds to the proportion of the total cost C_{tot} attributed to

each group q . By construction, $\sum_{q=1}^Q w_q = 1$ so that problem (1) is equivalent to:

$$\Xi^* = \arg \max_{\Xi} \det\left(C_{tot} \sum_{q=1}^Q w_q H_F(\xi_q)\right) \quad (2)$$

where Ξ is defined by a set of Q elementary designs and their associated frequency $\{(w_q, \xi_q), q=1, \dots, Q\}$, where ξ_1, \dots, ξ_Q are in S , the frequencies verify $0 \leq w_q \leq 1$ and

$\sum_{q=1}^Q w_q = 1$; $H_F(\xi_q)$ corresponds to the information per unit cost and is defined as

$$H_F(\xi_q) = \frac{M_F(\xi_q)}{C(\xi_q)}.$$

The numbers of subjects per group are derived from the proportions of cost w_q using

$$N_q = \frac{w_q C_{tot}}{C(\xi_q)} \text{ and rounded to integers, for a total cost of } \sum_{q=1}^Q N_q C(\xi_q).$$

Fedorov-Wynn algorithm

We use the Fedorov-Wynn algorithm, as in Mentré et al. (1997), to optimise designs with cost functions, as formalised in equation (2). Design optimisation problems formalised in equation (1) can also be solved by the same algorithm as it is a special case with constant costs. We provide a brief description of the algorithm here, referring interested readers to the book by Walter and Pronzato (1997) for details.

The Fedorov-Wynn algorithm relies on the Kiefer-Wolfowitz equivalence theorem, which states that the three following proposals are equivalent:

- (i) Ξ is D-optimal, i.e. $\det(M_F(\Xi))$ is maximal within the set of population designs generated by S
- (ii) $\max_{\xi \in S} d(\Xi, \xi) = P$
- (iii) Ξ minimises $\max_{\xi \in S} d(\Xi, \xi)$

where $d(\Xi, \xi)$ is a function of a population design Ξ and an elementary design ξ , defined below. Given a population design $\Xi = \{(w_q, \xi_q), q = 1, \dots, Q\}$, an elementary design ξ in S , and any w between 0 and 1, we can define a new design Ξ' by adding to Ξ an elementary design ξ with weight w and by multiplying w_1, w_2, \dots, w_Q by $(1-w)$. For simplicity, we write this as $\Xi' = (1-w)\Xi + w\xi$, confounding the elementary design ξ with the population design where all individuals have elementary design ξ . The information matrix of this design is $M_F((1-w)\Xi + w\xi)$. The function $d(\Xi, \xi)$ is then defined as the derivative of $\log(\det(M_F(\Xi')))$ taken at $w = 0$.

The equivalence theorem provides a way to construct the optimal design iteratively:

1. start with an initial guess Ξ_0
2. at step k , with the current design being Ξ_k ,
 - find $\xi^* = \arg \max_{\xi \in S} d(\Xi_k, \xi)$
 - stop if $\max_{\xi \in S} d(\Xi_k, \xi) \leq P + \rho$ where $\rho \ll 1$ is a predetermined tolerance
3. otherwise, update the design to $\Xi'_k = (1 - w^*)\Xi_k + w^*\xi^*$, where w^* is chosen over $(0,1)$

such that $w^* = \frac{(d(\Xi_k, \xi^*) - P)}{P(d(\Xi_k, \xi^*) - 1)}$
4. optimise the weights using an active set method with a projected gradient method for the selection of the direction, as in Mallet (1986), leading to design Ξ_{k+1} .

Steps 1-4 never remove an elementary design from Ξ_k . However, we know that, following the Caratheodory's theorem, there exists an optimal design which includes at most $P(P+1)/2$ different elementary designs (Fedorov (1972)). To control the number of elementary designs, an additional step is included in the algorithm after the optimisation of the weights to remove elementary designs with a weight lower than a predetermined δ (we chose $\delta = 10^{-8}$).

4. Design optimisation for the joint model of infliximab and methotrexate pharmacokinetics

In this section, we apply the Fedorov-Wynn algorithm with cost functions to design optimisation for a joint PK modelling of infliximab and methotrexate. The a priori values of the population parameters are fixed to those estimated previously in the litterature (Table I).

4.1. Design and cost function specifications

To allow comparison with the empirical design defined in Section 2.3, we use the same set of 12 possible times as for the empirical design. We only consider designs with the same sampling times for both drugs. The total cost C_{tot} is fixed to 1200 and the number of samples per patient is allowed to vary from 2 to 12.

To take into account different relative feasibilities in clinical practice, we define four different cost functions. The first cost function is a classical one, i.e. the cost of an elementary design is equal to its number of samples. For multiple responses, we define the number of samples for one elementary design as the sum of the number of samples for each response, even if several responses are measured from only one actual blood sample, reflecting the cost of the analysis rather than the cost of the act of sampling itself. We therefore define this cost function as simply $C_{samples}(\xi_i) = n_i$.

The second cost function, denoted C_{inconv} measures the inconvenience for the patient by penalizing late samples during the dose interval. Patients are kept in the hospital for 3 hours during the infusion of infliximab, therefore samples taken during the initial 3 hours of Day 1 of Week 1 are attributed an unitary cost of 1. During the same day, samples taken at 6 or 8 hours required the patient to stay for a further 3 or 5 hours and are given a cost of 2. The 24 hours sampling time requires the patient to return to the hospital the next day; it incurs a cost of 4. For times within Day 1 of Week 8, as patients also need to return to the hospital, we assume a cost of 3 for the visit, in addition to the cost of the samples themselves, which are set to those of Day 1 of Week 1. For each response, the second cost function is therefore

$$\text{computed as: } C_{inconv}(\xi_i) = \sum_{j,k} C_{time}(t_{ikj}) + C_{visit}(\xi_i)$$

where $C_{time}(t) = 1$ if $t = 0.5, 1$ or 3 ; $C_{time}(t) = 2$ if $t = 6$ or 8 ; $C_{time}(t) = 4$ if $t = 24$

$C_{visit}(\xi_i) = 3$ if ξ_i contains at least one of the times (0.5, 1, 3, 6, 8) of the second period, 0 otherwise.

The third cost function considers the inclusion of a new patient in the design as more costly than additional blood samples in patients already in the study. In this case, the cost of an elementary design is given by the number of sampling times penalised by a constant: $C_{patient}(\xi_i) = n_i + 12$. Choosing 12 for the cost of adding a new patient is equivalent to taking 6 additional blood samples in one patient since there are 2 responses.

Finally, the fourth cost function denoted $C_{inconv-patient}$ combines both the inconvenience of each sample with the cost of additional patients in the study:

$$C_{inconv-patient}(\xi_i) = \sum_{j,k} C_{time}(t_{ikj}) + C_{visit}(\xi_i) + 12.$$

4.2. Numerical implementation

The expression of M_F for a multiple response model with the first order approximation is implemented in PFIM 3.0, an extension of PFIM. The implementation considers only cases with diagonal variance matrix of the random effects and specific variance error models given as: $Var(\varepsilon_k) = diag(\sigma_{1k} + \sigma_{2k} f_k(g(\beta, b), \xi_k))^2$, where σ_{1k} and σ_{2k} qualify the model for the variance of the residual error of the k^{th} model. Furthermore, the implementation assumes that the variance of the observations with respect to the mean parameters is constant, which results in a block diagonal M_F , i.e., $(C(E, V))_{mn} = 0$ with $n = 1, \dots, \dim(\lambda)$ and $m = 1, \dots, \dim(\beta)$.

The Fedorov-Wynn algorithm is implemented in PFIM using a C code, and linked with R via a dynamic link library. Note that the current implementation for multiple response models as implemented in PFIM 3.0 does not require the same sampling times for the different responses, but runtimes may become prohibitively high for complex designs

4.3. Designs comparison

We then perform comparisons between the optimal population designs for the different cost functions. We compare the efficiency of the empirical design to the design optimised with the classical cost function on the total number of samples. To do that, we use the information function Φ classically used to compare efficiency between designs. Φ is defined as the determinant standardized by P , the dimension of the parameters vector Ψ^0 , $\Phi(\Xi) = \det(M_F(\Psi^0, \Xi))^{1/P}$. The relative efficiency of a population design Ξ_1 with respect to a population design Ξ_2 is given by $\Phi(\Xi_1)/\Phi(\Xi_2)$. This ratio can then be considered as the geometric mean of variance decrease using Ξ_1 instead of Ξ_2 .

Moreover, for each cost function, we compare the total cost of the four optimised designs and we investigate the cost-efficiency relation between the designs.

4.4. Results

The optimal designs are given in Table 2, with sampling times corresponding to measurements of the two drugs in the study. They are called $Opt_{samples}$, Opt_{inconv} , $Opt_{patient}$ and $Opt_{inconv-patient}$ corresponding to the four cost functions $C_{samples}$, C_{inconv} , $C_{patient}$ and $C_{inconv-patient}$, respectively. The optimal designs are different according to the cost functions used; they have different sampling times but also different group structures, with, for example a total number of patients ranging from 36 for $Opt_{inconv-patient}$ to 194 for $Opt_{samples}$.

$Opt_{samples}$ involves four elementary designs with an unequal repartition of the number of patients and of the number of samples per group; nearly 70% of the patients have only two samples compared to the empirical design with 12 samples to be performed in all the patients. The relative standard errors (RSE) for the empirical design and the design $Opt_{samples}$ are reported in Table 3; these RSE are defined as the standard error divided by the true value of

the parameter, expressed in %. Both designs allow good parameter estimate precisions for the infliximab parameters and the methotrexate fixed effects parameters (about or lower than 20%), with higher precision for $Opt_{samples}$. Some variance parameters of methotrexate cannot be accurately estimated with either design, but the expected RSE are in the same range for both designs.

Design Opt_{inconv} involves five elementary designs with 2 groups of only one patient. More than 60% of the subjects have samples only during the first three hours of Week 1, reflecting the penalties on the cost of the late samples. Only one group of 11 patients are scheduled for one sample at an additional visit (Week 8). Note that removing the two groups with only 1 patient would simplify the group structure of this design and would not involve any major loss of information with an information value of 134.3 instead of 135.2.

The optimisation taking into account of the difficulty of adding new patients provides an optimal design $Opt_{patient}$ with one group of only 37 patients, but with 5 sampling times at Week 1 to be repeated at Week 8.

Last, the optimisation taking into account both constraints of times allocation and patients provides a design with the smallest number of patients, and varying number of samples per patient from 4 to 7, mainly performed at Week 1.

Comparing designs using the information function Φ , we find the largest value for $Opt_{samples}$ (210.8) and the smallest for $Opt_{inconv-patient}$ (68.4), as expected because of its substantial cost constraints. Design $Opt_{inconv-patient}$ involves higher standard errors; they are still acceptable on the fixed effects, with values around or lower 20% except for the rate constant of absorption and the peripheral compartment volume with values around 25% and 35% respectively.

The comparison of the cost of each optimised designs using the different cost functions are reported on Figure 2. The design $Opt_{samples}$ in which no cost other than the number of samples is assumed, always incurs the highest cost of the four designs, whatever the cost function, with a cost of nearly 5500 for the cost function $C_{inconv-patient}$. Logically, the most constrained design $Opt_{inconv-patient}$ always incurs the lowest cost, with a cost of 440 for the cost function $C_{samples}$. The cost-efficiency relationship is represented on Figure 3 for the cost function $C_{inconv-patient}$, which is the most clinically realistic. Although the cost of a design can largely exceed the allowed total cost, the corresponding efficiency does not increase proportionally, which signals a waste of resources.

5. Discussion

In this paper, we find optimal designs for NLMEM with multiple responses using the Fedorov-Wynn algorithm with cost functions. The application to a joint PK model of infliximab and methotrexate, with very different time scales, nicely shows the benefit of design optimisation using cost functions, especially when substantial constraints on the design are imposed. Indeed, the optimal designs obtained with the four different cost functions are very different and reflect the penalties imposed on the times allocation and/or the group structure. Our work here shows that by combining a cost function with a user-specified set of possible sampling times, the Fedorov-Wynn algorithm is a powerful tool for finding optimal designs suitable to clinical applications.

The expression of M_F used to optimise design is based on a linearisation of the model.

Moreover, in our application, we use the block diagonal version of the approximated expression of M_F , assuming that the variance of the observations with respect to the mean parameters is constant. Although those are approximations, it has been shown for single response models (Retout et al. (2007)) and for multiple response models (Bazzoli et al.

(2007)) that the approximated M_F is very close to that computed by more exact methods, such as the Fisher matrix based on the Stochastic Approximation Expectation Maximisation (SAEM) algorithm implemented in MONOLIX (Kuhn et Lavielle (2005); Samson et al. (2006)). Indeed, using this software, evaluation of the expected SE can be performed under asymptotic convergence assumption. To do that, a data set with a large number of subjects is simulated, the parameters are then estimated as well as the observed Fisher information matrix on the simulated data set using the Louis's principle (Louis (1982)). Expected SE are then obtained by rescaling of the observed SE to the true number of subjects. Although this exact method does not involve any linearization, it is time consuming, and it cannot then be applied to design optimisation. The linearisation is thus a great advantage for optimisation process where a large number of designs have to be evaluated in a reasonable time-frame. In our application, we consider computation of M_F only for a diagonal variance of the random effects; however, in practice, one may want to allow correlation between the random effects. Although the proposed expression of M_F allows those correlations, it has not been yet implemented in PFIM. In our example the models for infliximab and methotrexate PK do not share any parameter, but the expression of M_F for multiple response models can be used for more complex modelling, including models with common parameters, such as models for the PK of a parent drug and of its metabolites, drug interactions or PK/PD models. Here, for simplicity, we assumed the same sampling times for the two drugs. In some cases, different sampling times for the two responses may be required; the Fedorov-Wynn algorithm can be used under this assumption but the number of possible elementary designs will quickly become prohibitively large and can considerably increase the computation time and memory requirement can become a problem.

This Fedorov-Wynn algorithm has been implemented to find the optimal design with a number of groups lower than the bound of the Caratheodory's theorem. Other optimal designs

with higher number of groups, although possible, are not considered here because they would be very difficult to implement in clinical settings.

In our application, most of the optimised designs lead to several groups of subjects with different number of subjects for the different groups. In addition to the influence of the cost functions, this may also be related to the small intra-individual correlation, which has been shown to lead to imbalance (van Breukelen et al. (2008)).

The numbers of subjects per group has been rounded to the nearest integer. This was mainly to keep the total cost as close to 1200 as possible, in order to achieve comparable designs with same total cost, but it is obvious that, in clinical practice, this number should be rounded to the nearest five or even to the nearest ten. Depending on the cost function used, this could change the total cost of the design and care should be taken to avoid a substantial cost overrun.

We conclude by noting that attention has to be given to the cost function used. Indeed, a too strict cost function with high penalisation may considerably decrease the efficiency of a design, as illustrated by the design $Opt_{inconv-patient}$ compared to the design $Opt_{samples}$. It is then important to strike a proper balance between the clinical constraints and the information that really needs to be collected from the study to obtain reliable results. From a decision-making point of view, design optimisation including costs can be a very valuable tool to assess both the clinical consequences and the cost-effectiveness of a candidate design: we can show the efficiency of a design optimised under given constraints, and also immediately compute the cost of adding more patients or redesigning the study. This is useful because the trade-off between total cost and efficiency is now clear. Consequently, a go or no-go decision can be made with confidence.

The Fedorov-Wynn algorithm with the usual cost function, equal to the total number of samples, is available in PFIM 3.0 for single and multiple response models. The version

including the possibility to specify user-defined cost-functions will be available in version 3.1 of the PFIM software, and in the meantime, can be obtained from the authors on request.

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Legends for figures

Figure 1. Kinetic profile of infliximab and methotrexate at steady state for the mean parameters described in Table 1. The sampling times at Week 1 and Week 8 of the empirical design are shown as *.

Figure 2. Cost of the four optimised designs under each cost function. The dotted line represents the reference cost of 1200.

Figure 3. Relative cost versus relative efficiency for the four optimised designs considering the cost function $C_{inconv-patient}$. Efficiencies and costs are given relatively to the efficiency and cost of the most constrained design $Opt_{inconv-patient}$. The optimised designs $Opt_{samples}$, Opt_{inconv} , $Opt_{patient}$ and $Opt_{inconv-patient}$ are represented by \times , *, \blacksquare , and \blacktriangle respectively. The full line represents the unity line.

Table 1. Mean values and interpatient variability for infliximab (Kavanaugh et al. (2000)) and methotrexate parameters (Godfrey et al. (1998)).

	Parameter	Mean	Interpatient variability (CV%)
<i>infliximab</i>	Cl (l/h)	0.01	63.0
	V (l)	4.3	58.0
<i>methotrexate</i>	k_a (h^{-1})	3.67	76.7
	Cl (l/h)	7.34	27.2
	V_c (l)	23.5	27.9
	V_p (l)	25.3	31.2
	Q (l/h)	4.25	40.5

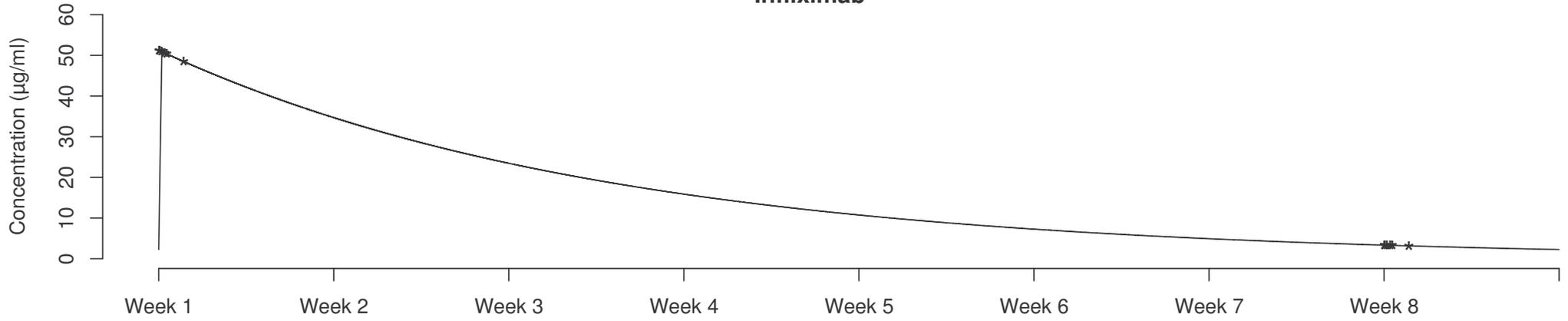
Table 2. Optimal population designs for the joint model of infliximab and methotrexate according to different cost functions (for each design, Q is the number of elementary designs and N_q the rounded number of subjects with the elementary design ξ_q). Elementary designs are shown only once, but correspond to samples taken for both drugs.

Design	Q	Elementary designs		N_q	Information value $\Phi(\Xi)$
		ξ_q (hr)			
		Week 1	Week 8		
<i>Empirical</i>		0.5, 1, 3, 6, 8, 24	0.5, 1, 3, 6, 8, 24	50	157.8
<i>Opt_{samples}</i>	4	1	0.5	92	210.8
		3	8	42	
		6, 24	24	30	
		0.5, 1, 3, 8, 24	3, 8, 24	30	
<i>Opt_{inconv}</i>	5	0.5, 1, 3	-	85	135.2
		0.5, 1, 3, 8	-	35	
		0.5, 1, 3, 6, 8, 24	24	11	
		0.5, 1	-	1	
		0.5, 3	-	1	
<i>Opt_{patient}</i>	1	0.5, 1, 3, 8, 24	0.5, 1, 3, 8, 24	37	107.0
<i>Opt_{inconv-patient}</i>	5	0.5, 1, 3, 8	0.5, 1, 3	11	68.4
		0.5, 1, 3, 6, 8	24	9	
		0.5, 1, 3, 6, 8, 24	24	8	
		0.5, 1, 3, 8	-	7	
		0.5, 1, 3, 8	24	1	

Table 3. Relative standard errors (RSE) evaluated from the Fisher information matrix for the empirical design and the design $Opt_{samples}$.

Parameters		RSE (%)	
		Empirical	$Opt_{samples}$
<i>infliximab</i>	Cl	9.0	4.6
	V	8.3	4.4
	ω_{Cl}^2	20.2	10.6
	ω_V^2	20.5	11.3
	σ_2	3.2	4.9
<i>methotrexate</i>	k_a	18.5	16.0
	Cl	5.3	4.5
	V_c	6.5	5.6
	V_p	17.5	16.7
	Q	14.8	14.8
	$\omega_{k_a}^2$	39.3	38.6
	ω_{Cl}^2	27.4	28.0
	$\omega_{V_c}^2$	32.5	28.5
	$\omega_{V_p}^2$	222.4	273.6
	ω_Q^2	87.6	103.2
	σ_1	7.6	8.2
	σ_2	7.4	10.2

Infliximab



Methotrexate

