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RESEARCH PAPER

Influence of the Size of Cohorts in Adaptive Design for Nonlinear Mixed Effects Models: An Evaluation by Simulation for a Pharmacokinetic and Pharmacodynamic Model for a Biomarker in Oncology

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ABSTRACT

Purpose In this study we aimed to evaluate adaptive designs (ADs) by clinical trial simulation for a pharmacokinetic-pharmacodynamic model in oncology and to compare them with one-stage designs, i.e., when no adaptation is performed, using wrong prior parameters.

Methods We evaluated two one-stage designs, ξ_0 and ξ_*, optimised for prior and true population parameters, Ψ_0 and Ψ^*, and several ADs (two-, three- and five-stage). All designs had 50 patients. For ADs, the first cohort design was ξ_0. The next cohort design was optimised using prior information updated from the previous cohort. Optimal design was based on the determinant of the Fisher information matrix using PFIM. Design evaluation was performed by clinical trial simulations using data simulated from Ψ^*.

Results Estimation results of two-stage ADs and ξ_* were close and much better than those obtained with ξ_0. The balanced two-stage AD performed better than two-stage ADs with different cohort sizes. Three- and five-stage ADs were better than two-stage with small first cohort, but not better than the balanced two-stage design.

Conclusions Two-stage ADs are useful when prior parameters are unreliable. In case of small first cohort, more adaptations are needed but these designs are complex to implement.

KEY WORDS adaptive design · Fisher information matrix · nonlinear mixed effects model · optimal design · pharmacokinetic-pharmacodynamic

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ABBREVIATIONS

AD	Adaptive design
FIM	Fisher information matrix
NLMEM	Nonlinear mixed effects model
PD	Pharmacodynamic
PK	Pharmacokinetic
REE	Relative estimation error
RRMSE	Relative root mean squared error
TGF-β	Transforming growth factor β

INTRODUCTION

Nonlinear Mixed Effects Models (NLMEM) [1] are increasingly performed for analysis of pharmacokinetic and pharmacodynamic (PKPD) data of preclinical or clinical studies [2, 3] in drug development and drug use.

The design of a so-called population PKPD study, that is the number of patients, the sampling times for each patient and their allocation in time, plays an important role on parameter estimation [4]. Choosing a good design when planning a study is essential and it is a crucial step as poor design can lead to inconclusive studies. For the evaluation and optimisation of population designs, the first approach was clinical trial simulation, which involves parameter estimation and thus is a time-consuming method [5]. The approach that avoids simulations, based on the Fisher information matrix (FIM) for NLMEM utilizing first-order (FO) linearisation method [6], has been first proposed by Mentré *et al.* in 1997 and several developments have been done since then. Different software are in use to perform optimal design in NLMEM [7, 8]; these are: PFIM [9, 10], PopED [11], PopDes [12], POPT [13]. Within those, one can evaluate the different designs by computing FIM and perform design optimisation based on the D-optimality criterion, i.e., maximization of the determinant of FIM. Furthermore, it was shown in [8] that all software

provided with the same answer using the same FO approximation of FIM.

Optimal designs depend on *a priori* information, both on models and parameters, which can be partially wrong as they may be difficult to guess. Currently, population designs are often fixed for the whole study with data analyzed at its end. Local optimal designs are optimised based on a set of parameters values known *a priori*, whereas in robust optimal designs [14–16], a prior parameter distribution is defined.

Adaptive designs (ADs) are promising alternatives to local or robust designs [17]. As opposite to traditional clinical studies, ADs are clinical trial designs that 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 [18, 19]. This is very important, for instance when designing a clinical trial, having only prior information on preclinical data, or designing a study in children from adults information. ADs are useful to provide some flexibility during the design but were rarely used for NLMEM [20]. Nevertheless, according to a survey by Mentré *et al.*[7], adoption of adaptive design approach for population PKPD studies is promising in pharmaceutical industries. It was shown, in previous studies not concerning NLMEM, that two-stage designs could be more efficient than fully adaptive designs [21] when the adaptation is performed after each patient. Chen *et al.*[22] compared three- *versus* two-stage AD. They found that the gain of extending a two-stage design approach to three-stage design is not as relevant as compared to the advantage of using two-stage instead of one-stage design. Moreover, two-stage designs are easier to implement in clinical practice as only one adaptation is performed.

Some important steps in AD are choosing the number of stages one wants to compute, i.e., the number of times parameters estimation and adaptations will be performed, and the cohort size to be set for each stage.

For NLMEM, Dumont *et al.* [23] implemented the optimisation of the determinant of FIM for two-stage adaptive designs. In that paper [23] a simulation study that mimicked the design of a pediatric PK trial was used and it was analyzed through NLMEM. For the first stage, parameters were guessed from adults. Simulations of one- and two-stage designs were evaluated assuming that some parameters were different than the initial ones. They showed the applicability and usefulness of the approach that we wish to further investigated in this study in a more complex example.

The example used for this study concerns a PKPD model in oncology, based on the SMAD phosphorylation (pSMAD) biomarker, and developed for a novel oral transforming growth factor β (TGF-β) inhibitor [12, 24]. TGF-β, plays an important role on regulation of many physiological processes. TGF-β signalling leads to phosphorylation of SMAD complexes which stimulates transcription of TGF-β responsive gene. The compound LY2157299, that is a small molecule TGF-β inhibitor, inhibits the TGF-β induced Smad phosphorylation [25].

The objective of the present work is to evaluate by clinical trial simulation two-stage ADs for this model and compare them with one-stage designs, i.e., when no adaptation is performed, when wrong prior parameters are used. We then studied the influence of the size of each cohort in two-stage ADs. Finally we studied extensions of two-stage AD, not yet investigated in NLMEM, as three- and five-stage ADs. We used the new release of PFIM 4.0, where prior information can be incorporated on FIM evaluation and/or optimisation in order to perform adaptive design [10, 23].

MATERIALS AND METHODS

Standard NLMEM

In NLMEM, the vector of observations y_i for the i^{th} individual is described by a function f that depends nonlinearly on the p-sized vector of individual parameters ϕ_i and on the elementary design ξ_i of n_i sampling times $(t_{i1}, ..t_{n_i})$ then $y_i = f(\phi_i, \xi_i) + \epsilon_i$. The model can also be defined as $y_i = f(g(\beta, b_i), \xi_i) + \epsilon_i$, with $\phi_i = g(\beta, b_i)$, where β is the p-sized vector of fixed effects parameters, b_i are the random effects assumed normally distributed with zero mean and variance Ω. The standard functions for g are $g(\beta, b_i) = \beta + b_i$ and $g(\beta, b_i) = \beta \times \exp(b_i)$, corresponding to additive or exponential random effects, respectively. Here it is further assumed that Ω is a $p \times p$ diagonal matrix with diagonal elements the variances $\omega_s^2, s = 1,..,p$ each one corresponding to the variance of the s^{th} component of the vector b_i. The n_i -vector of residual errors ϵ_i is normally distributed with zero mean and variance equal to $\Sigma(\beta, b_i, \sigma_{\text{inter}}, \sigma_{\text{slope}}, \xi_i) = \text{diag}(\sigma_{\text{inter}} + \sigma_{\text{slope}} \times f(g(\beta, b_i), \xi_i))^2$, where σ_{inter} and σ_{slope} are the standard deviations of the additive and proportional components respectively.

The vector of the population parameter Ψ is composed of the vector of fixed effects β and the vector of variance terms $\lambda' = (\omega_1^2, \ldots, \omega_p^2, \sigma_{\text{inter}}, \sigma_{\text{slope}})$, such that $\Psi' = (\beta', \lambda')$.

Adaptive Population Design

A fixed population design Ξ, i.e., a one-stage design, is defined by the total number N of individuals and the set of individual elementary designs to be performed in each individual: $\xi_1, \ldots, \xi_N$ with a total number of observations $n_{tot} = \sum_{i=1}^{N} n_i$, so that $\Xi = \{\xi_1, \ldots, \xi_N\}$. A special case is when the same elementary design is performed in all individuals ($\xi_i = \xi$ for $i = 1, \ldots, N$), then $n_{tot} = n \times N$ and $\Xi = \{\xi; N\}$. In the case of K-stage design, K population designs are defined for $N_1, \ldots, N_K$ groups of individuals ($N_1 + \ldots + N_K = N$) and are denoted by $\Xi_1, \ldots, \Xi_K$.

In this work, the following assumptions were made: i) the same elementary design ξ_k is performed for all individuals

within each cohort k; ii) the size of each cohort N_k ($k=1,\ldots,K$) is fixed, and iii) the number of sampling times n in each elementary design is fixed and is the same for each cohort.

The K-stage adaptive design schema is shown in Fig. 1 and the approach can be defined as follows. For the first stage, data Y_1 are collected for N_1 individuals with a prior design ξ_1 optimised from prior parameters Ψ_0. Population parameters $\widehat{\Psi}_1$ are then estimated from the collected data. At the k^{th} stage, data Y_k are collected for N_k individuals with design ξ_k, where ξ_k is optimised using parameter estimates $\widehat{\Psi}_{k-1}$. Population parameters $\widehat{\Psi}_k$ can thus be estimated with both data $Y_1,\ldots,Y_k$ gathered together from $N_1+\ldots+N_k$ individuals. The process of adaptation continues until the last step, that is the K^{th} stage, where the final parameters $\widehat{\Psi}_K$ are estimated using data $Y_1,\ldots,Y_k,\ldots,Y_K$, collected for $N_1+\ldots+N_k+\ldots+N_K=N$ individuals.

Several approaches can be used for design optimisation, here D-optimality criterion was used, which is the maximisation of the determinant of the Fisher information matrix.

Fisher Information Matrix

Let $l(\Psi\,|\,y)$ be the log-likelihood of the vector of observations y for an individual (the index i is omitted for simplicity) for the population parameters Ψ. The elementary FIM for that individual with design ξ is defined as

$$M_F(\Psi,\xi)=E\left(-\frac{\partial^2 l(\Psi|y)}{\partial\Psi\partial\Psi'}\right). \quad (1)$$

Because of nonlinearity of the model $f(g(\beta,b),\xi)$, there is no analytical expression of the log-likelihood and therefore of FIM. Several approaches have been developed in the years to compute FIM. Although there is no clear consensus on what is the best approximation, in this approach by FO linearization of the structural model around the random effects it is assumed the choice of block diagonal expression [8, 26].

As shown in Dumont *et al.* [23], in adaptive design, the population FIM in the first stage can be written as

$$M_F^1=M_F(\Psi_0,N_1\xi)=N_1M_F(\Psi_0,\xi) \quad (2)$$

A design ξ_1 maximises the determinant of M_F^1.

At the k^{th} stage, using parameters estimates from the previous stage ($\widehat{\Psi}_{k-1}$), the design ξ_k corresponds to the maximum of the determinant of Fisher information matrix M_F^k, where

$$\begin{aligned}M_F^k&=M_F\left(\widehat{\Psi}_{k-1},N_1\xi_1+\cdots+N_{k-1}\xi_{k-1}+N_k\xi\right)\\&=N_1M_F\left(\widehat{\Psi}_{k-1},\xi_1\right)+\cdots+N_{k-1}M_F\left(\widehat{\Psi}_{k-1},\xi_{k-1}\right)\\&\quad+N_kM_F\left(\widehat{\Psi}_{k-1},\xi\right)\end{aligned} \quad (3)$$

so that

$$\xi_k=\underset{\xi}{argmax}\left(\det\left(M_F^k\right)\right) \quad (4)$$

The process continues until the last stage (K) where the population FIM can be written as:

$$\begin{aligned}M_F^K&=M_F\left(\widehat{\Psi}_{K-1},N_1\xi_1+\cdots+N_{K-1}\xi_{K-1}+N_K\xi\right)\\&=N_1M_F\left(\widehat{\Psi}_{K-1},\xi_1\right)+\cdots+N_{K-1}M_F\left(\widehat{\Psi}_{K-1},\xi_{K-1}\right)\\&\quad+N_KM_F\left(\widehat{\Psi}_{K-1},\xi\right)\end{aligned} \quad (5)$$

and ξ_K is the optimal design for M_F^K:

$$\xi_K=\underset{\xi}{argmax}\left(\det\left(M_F^K\right)\right) \quad (6)$$

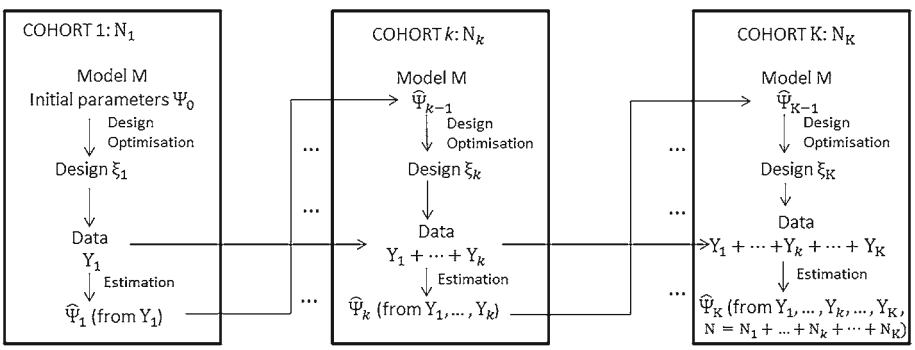

Fig. 1 Schema of K-stage adaptive design.

Simulation Study

The example used in this study is based on a PKPD model published in [12] for the compound LY2157299, a small molecule TGF-β inhibitor. A single oral daily dose of 80 mg was considered.

In the model reported in the literature, the PK was modelled by a one-compartment first-order absorption model given by:

$$C(t) = \frac{D}{V}\frac{k_a}{k_a - (CL/V)}\left(e^{-(CL/V)\cdot t} - e^{-k_a t}\right) \quad (7)$$

where D is the dose, k_a is the first order rate constant of absorption, V is the volume of distribution, CL is the clearance. Please note that CL and V are apparent volume and clearance. As there is no data after intravenous administration, bioavailability of typical individual was set to 1. The inhibition of TGF-β signalling by the treatment is represented by a turnover model [12], that is a simplification of the semi-mechanistic model developed by Bueno *et al.*[24]:

$$\frac{dR(t)}{dt} = k_{syn}\left(1 - I_{max}\frac{C(t)}{C(t) + IC_{50}}\right) - k_{out}R(t) \quad (8)$$

where R(t) is the quantity of pSMAD (correlated to TGF-β activity); k_{syn} and k_{out} are a zero order rate constant of synthesis and a first order rate constant of degradation of pSMAD, respectively, and IC_{50} is the concentration necessary to achieve 50% maximum inhibition. The maximum inhibitory response I_{max} was set to 1. A graphical representation of the model is shown in Fig. 2.

The PD used in the modelling is I(t), the relative inhibition of TGF-β defined by:

$$I(t) = \frac{R_0 - R(t)}{R_0} \quad (9)$$

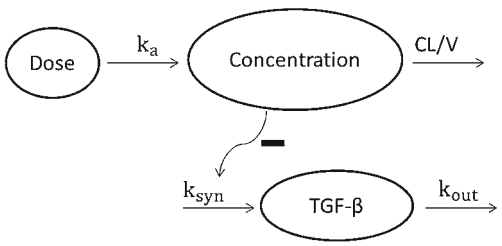

Fig. 2 Graphical representation of the PKPD model.

where R_0 is the baseline pSMAD equal to $\frac{k_{syn}}{k_{out}}$. The PD model is therefore rewritten as follow:

$$\frac{dI(t)}{dt} = k_{out}\, I_{max}\frac{C(t)}{C(t) + IC_{50}} - k_{out}I(t) \quad (10)$$

Two sets of PK and PD parameter values were defined for this study (Table I): prior (wrong) parameters Ψ_0 and true parameters Ψ^*. Prior parameters for PK were those coming from a PK analysis for the clinical study [25], whereas for the PD, similar values to those obtained in a preclinical study [24] were assumed. Concerning the true parameters Ψ^*, it was assumed that prior values were correct except for CL and k_{out} which were set to be four fold smaller and ten folds smaller, respectively. The PKPD model for the two sets of parameters is displayed in Fig. 3.

Exponential random effect model was chosen for all parameters with similar inter-individual variability of 70% except for k_a whose variability was set to 0. Proportional error model and additive error model were assumed for PK and PD respectively, with σ_{prop} and σ_{inter} set to 0.2.

Evaluated Designs

Several one-stage designs, i.e., non-adaptive designs, various two-stage ADs, two three-stage and one five-stage ADs were considered for a total number of N = 50 patients.

The evaluated one-stage designs were: first a rich design, ξ_{rich}, with $n = 6$ sampling times, 0.1, 0.5, 1.5, 4, 6, 12 h for both

Table I PK and PD Parameter of the Oncology Model Used in the Simulation Studies: Prior (Ψ_0) and True (Ψ^*)

PK Parameters	Prior (Ψ_0)	True (Ψ^*)
k_a (h^{-1})	2	2
V (L)	100	100
CL (L h^{-1})	**40**	**10**
$\omega^2_{k_a}$	0	0
ω^2_V	0.49	0.49
ω^2_{CL}	0.49	0.49
$\sigma_{inter,PK}$	0	0
$\sigma_{slope,PK}$	0.2	0.2
PD Parameters		
k_{out} (h^{-1})	**2**	**0.2**
IC_{50} (mg L^{-1})	0.3	0.3
$\omega^2_{k_{out}}$	0.49	0.49
$\omega^2_{IC_{50}}$	0.49	0.49
$\sigma_{inter,PD}$	0.2	0.2
$\sigma_{slope,PD}$	0	0

PK and PD; then two optimal designs with $n=3$ samples among the $n=6$ sampling times in ξ_{rich} that could differ between PK and PD. These designs are: ξ_0, D-optimal design for the prior parameters Ψ_0 and ξ_*, D-optimal design for the true parameters Ψ^*. For ξ_0 the optimal sampling times were for PK: 0.1, 4, 12 h and for PD: 0.5, 1.5, 4 h. For ξ_* the optimal sampling time were for PK: 0.1, 4, 12 h and for PD: 4, 6, 12 h. It should be noted that they are similar for PK and rather different for PD. A mixed design ξ_{0*} with N_1 =25 patients with design ξ_0 and N_2 =25 patients with design ξ_* was also evaluated. ξ_{0*} can be considered as a special case of two-stage design that would occur in the ideal case of estimating after the first stage the exact set of true parameters values, that is $\widehat{\Psi}_1 = \Psi^*$. Graphs of PK and PD simulated models with parameters Ψ_0 and Ψ^* and optimal designs ξ_0 and ξ_* are shown in Fig. 3.

The two-stage designs evaluated in this study were: first a balanced design ξ_{25-25} with the same cohorts size, i.e., same number of patients in the two cohorts: $N_1 = N_2 = 25$; then various unbalanced designs with different sizes in the two cohorts: ξ_{10-40}; ξ_{15-35}; ξ_{35-15}; ξ_{40-10}, where the first two designs have fewer patients in the first cohort whereas the second two designs have greater first cohort size.

The two three-stage designs considered have 10 patients in the first cohort: $\xi_{10-20-20}$ and $\xi_{10-10-30}$, whereas the five-stage design is $\xi_{10-10-10-10-10}$ with $N_1 = N_2 = N_3 = N_4 = N_5$ =10 patients.

All adaptive designs (two-, three- and five-stage) start by having the first design ξ_1 equal to the prior design ξ_0 for the first cohort.

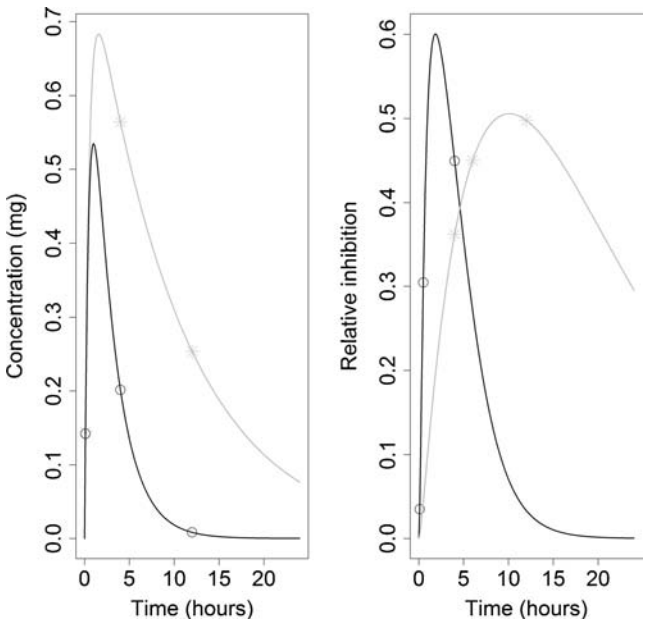

Fig. 3 PK (*left*) and PD (*right*) simulated models for a total daily dose of 80 mg, with prior parameters Ψ_0, in dark, and optimal sampling times ξ_0, in ○, and with true parameters Ψ^*, in grey, and optimal sampling times ξ_*, in *.

Clinical Trial Simulation and Designs Comparison

One hundred datasets of N=50 patients were simulated with the true parameters Ψ^* and design ξ_{rich} described in the section above. In order to get datasets for the other designs only the corresponding sampling times were selected from the dataset of ξ_{rich}.

Design optimisation was performed using PFIM 4.0 [10, 23]. Adaptive designs were implemented in PFIM 4.0 [10, 23] thanks to the new features that allow for saving FIM and for considering previous information, i.e., previous FIM, in the calculation of FIM.

Parameters estimation was performed with the Stochastic Approximation Expectation Maximisation (SAEM) algorithm in the software MONOLIX 4.3 [1], with five chains and initial parameters estimates Ψ_0. By linking through an R code PFIM 4.0 and Monolix 4.3, it was thus possible to perform K-stage adaptive design.

In order to compare the designs in terms of the precision of parameter estimates, relative estimation error (REE) and relative root mean squared error (RRMSE) were calculated from the $R=100$ final parameters estimates for 50 patients and for each design considered in this study:

$$REE\left(\Psi_q^r\right) = \frac{\widehat{\Psi}_q^r - \Psi_q^*}{\Psi_q^*} \times 100 \tag{11}$$

$$RRMSE\left(\Psi_q\right) = \sqrt{\frac{1}{R}\sum_{r=1}^{R}\left(\frac{\widehat{\Psi}_q^r - \Psi_q^*}{\Psi_q^*}\right)^2} \times 100 \tag{12}$$

In those expressions, $\widehat{\Psi}_q^r$ represents the q^{th} estimated population parameter from the r^{th} simulated dataset, and Ψ_q^* is the correspondent true parameter value.

Furthermore, standardized RRMSEs [23] were computed for each design and each population parameter using as reference the RRMSE obtained with the best optimal one-stage design ξ_* optimised with the true parameters Ψ^*. More precisely the RRMSE associated to each parameter for a given design was divided by the corresponding RRMSE obtained with ξ_*, optimised with the true parameters Ψ^*. Means of the standardized RRMSEs across all parameters were also calculated and the closer they are to 1 the better is the design performance.

Estimated Optimal Designs for Various Adaptive Designs

For the 100 clinical trial simulations and for each studied adaptive design, the optimised designs of each cohort (except the first one which is fixed to ξ_0) were studied and it was also

compared how many elementary designs differed and how many were equal to the optimal design ξ_*.

RESULTS

One- and Two-Stage designs

Boxplots of the REEs for PK parameters k_a and CL, and PD parameters k_{out} and IC_{50}, for the various one-stage designs and the balanced two-stage adaptive design ξ_{25-25} are presented in Fig. 4. As expected, as design ξ_0 and ξ_* for PK are similar, estimation of PK parameters was found good for all designs and medians are close to 0. Different conclusions were drawn from the boxplots for PD parameters, where the medians REEs for the one-stage design ξ_0 in parameters k_{out} and IC_{50} were very large (about 30% and 50%, respectively), showing a systematic bias. Good results were obtained for ξ_* as expected, and also for the mixed design ξ_{0*} and for the balanced two-stage design ξ_{25-25}. Those results were confirmed by the RRMSE values and the standardized RRMSEs to those of ξ_* (Table II). RRMSE values for PK parameters were similar to those of ξ_* in all designs. For PD parameters, large RRMSE values were obtained for design ξ_0, with value larger than 2 for mean standardized RRMSE, whereas good results were observed for design ξ_{25-25} and design ξ_{0*}, similarly to those obtained with ξ_*, except somehow for IC_{50} and $\omega^2_{IC_{50}}$.

Influence of the Size of each Cohort in Two-Stage Adaptive Designs

Boxplots of REEs of PK and PD parameters for the various two-stage adaptive designs are presented in Fig. 5 and RRMSEs are presented in Table III. As before, there is a good

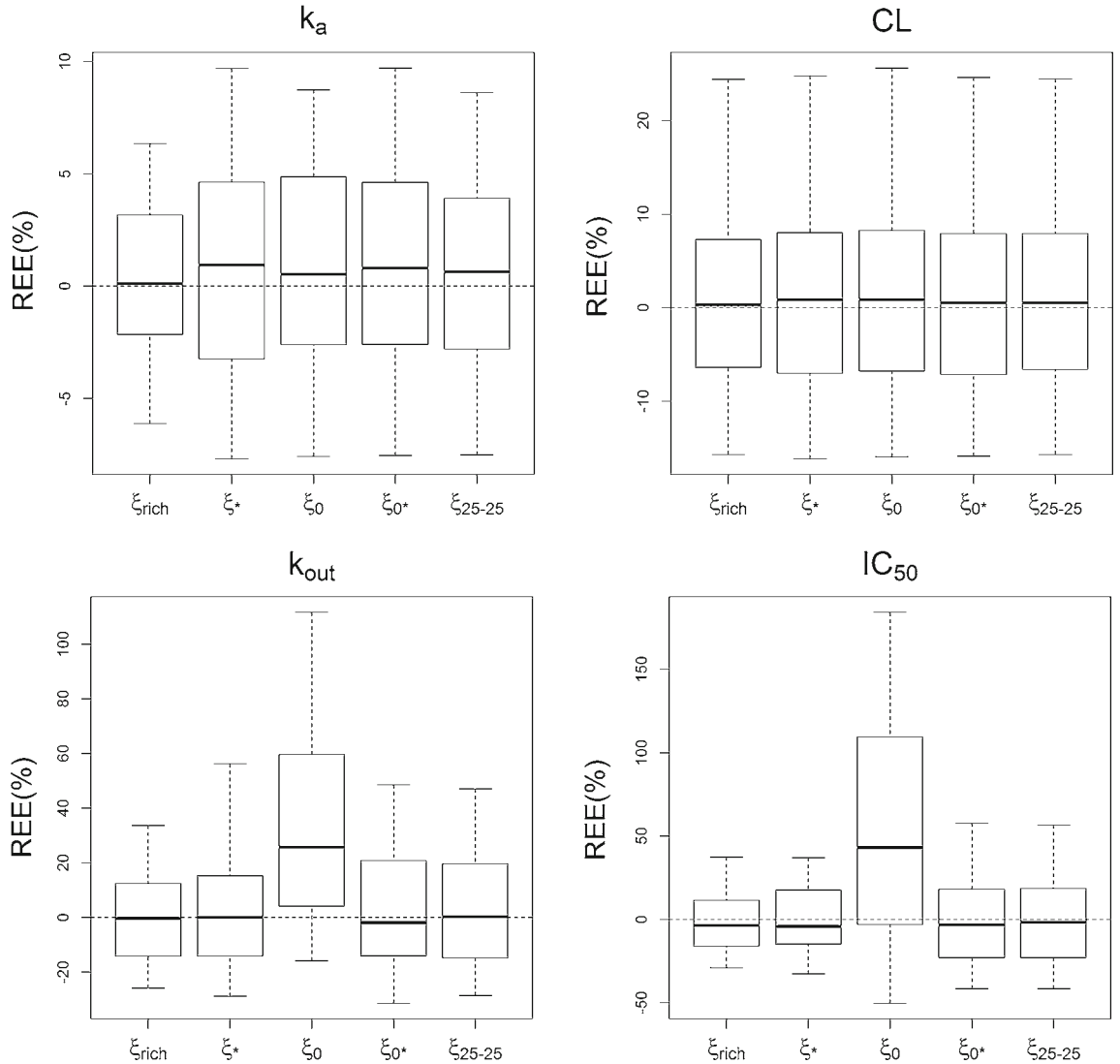

Fig. 4 Boxplot of relative estimation error (REE) for PK parameters k_a and CL (*top panel*) and PD parameters k_{out} and IC_{50} (*bottom panel*) in four one-stage designs and a balanced two-stage adaptive design.

Table II RRMSE % (and Standardized RRMSE with Respect to ξ_*) of Final Estimated Parameters in One-Stage Design and in Balanced Two-Stage Adaptive Design (N = 50 Patients)

	RRMSE % (standardized RRMSE)			
Parameters	ξ_*	ξ_0	ξ_{0*}	ξ_{25-25}
k_a (h^{-1})	5.8	5.6 (0.97)	5.7 (0.98)	5.0 (0.86)
V (L)	9.9	9.9 (1.00)	9.9 (1.00)	9.3 (0.94)
CL (L h^{-1})	12.5	12.4 (0.99)	12.5 (1.00)	12.5 (1.00)
ω^2_V	22.8	22.5 (0.99)	22.5 (0.99)	22.2 (0.97)
ω^2_{CL}	24.6	24.7 (1.00)	24.4 (0.99)	24.3 (0.99)
$\sigma_{slope,PK}$	10.1	10.2 (1.01)	10.0 (0.99)	9.9 (0.98)
k_{out} (h^{-1})	23.8	**54.5** (**2.29**)	25.4 (1.07)	24.1 (1.01)
IC_{50} (mg L^{-1})	22.1	**91.3** (**4.13**)	30.4 (1.38)	30.3 (1.37)
$\omega^2_{k_{out}}$	76.0	59.5 (0.78)	59.2 (0.78)	60.9 (0.80)
$\omega^2_{IC_{50}}$	72.2	**709.8** (**9.83**)	95.3 (1.32)	98.6 (1.37)
$\sigma_{inter,PD}$	7.3	6.4 (0.88)	6.3 (0.86)	6.2 (0.85)
Mean Standardized RRMSE	1.00	**2.17**	1.03	1.01

RRMSE in *bold* have at least a two-fold increase standardized RRMSE

precision of PK parameters estimates among all designs, whereas for PD parameters some differences between designs are noticeable, with a better result for the balanced two-stage adaptive design ξ_{25-25}. Results of RRMSEs and standardized RRMSEs for the various two-stage adaptive designs (Table III), confirmed a better performance of design ξ_{25-25}, and worst performance of designs with a larger sample size in the first cohort (ξ_{35-15} and ξ_{40-10}), where indeed the design adaptation is performed in only a small number of patients.

Two-, Three- and Five-Stage Adaptive Designs

Finally we compared two-, three- and five-stage ADs all with same number of patients in the first cohort (N_1 =10). Mean of standardized RRMSEs was smaller with the three-stage design $\xi_{10-20-20}$ and the five-stage design $\xi_{10-10-10-10-10}$, compared to the two-stage design ξ_{10-40} and the three-stage design $\xi_{10-10-30}$ (Table IV). Overall, ξ_{10-40} performed less well than the two three- and one five-stage designs considered, but those three- and five-stage designs were not better than the balanced two-stage design ξ_{25-25}. Furthermore, the five-stage design was not better than the best three-stage design $\xi_{10-20-20}$.

Comparison of Optimal Designs at each Step in Adaptive Design

Considering all adaptive designs, the number of different designs for the second cohort was the largest (12 different designs in 100 datasets) when the first cohort had only 10 patients, and was only 6 for design with larger first cohort (Table V).

For the two-stage ADs, the greatest number of datasets with optimal designs ξ_2 equal to ξ_* was obtained in the balanced two-stage AD ξ_{25-25} (Table V). Large numbers were also obtained for designs ξ_{35-15} and ξ_{40-10} but only a small sample of patients was affected in the second stage (15 and 10 patients, respectively), which explains the bad performance of the two designs (Table III).

In three-stage designs the greatest number of simulated datasets with optimal designs ξ_2 equal to ξ_*, was obtained for designs with smaller sample size in the second cohort ($\xi_{10-10-30}$) (Table V), whereas a greater number of optimal designs ξ_3 equal to ξ_* was obtained for the design that performed better, that is $\xi_{10-20-20}$.

Considering the first three stages of the five-stage design, results are similar to those obtained with the three-stage design $\xi_{10-10-30}$ with the same greatest number of simulated datasets with optimal designs ξ_2 equal to ξ_* and with only one design ξ_3 equal to ξ_* less, but in five-stage design fewer patients were used (only 30 in the first three stages, *versus* the 50 patients included in the three-stage design). For the fourth stage of five-stage designs the number of ξ_4 equal to ξ_* is smaller than the number of ξ_3 equal to ξ_* in the three-stage design $\xi_{10-20-20}$, whereas the number of ξ_5 equal to ξ_* in the fifth stage is slightly bigger than the number of optimal designs equal to ξ_* in the third stage of $\xi_{10-20-20}$, and this could explain why results of RRMSEs for the five-stage designs were similar to those obtained with $\xi_{10-20-20}$.

DISCUSSIONS

Two-stage AD in NLMEM was developed and implemented by Dumont *et al.* [23]. They have compared by simulation one-stage design, i.e., no adaptive design, with two-stage design, for a PK model in paediatrics simulation study, showing the importance of the adaptive design method if poor prior information is available. One point of discussion in their work was the

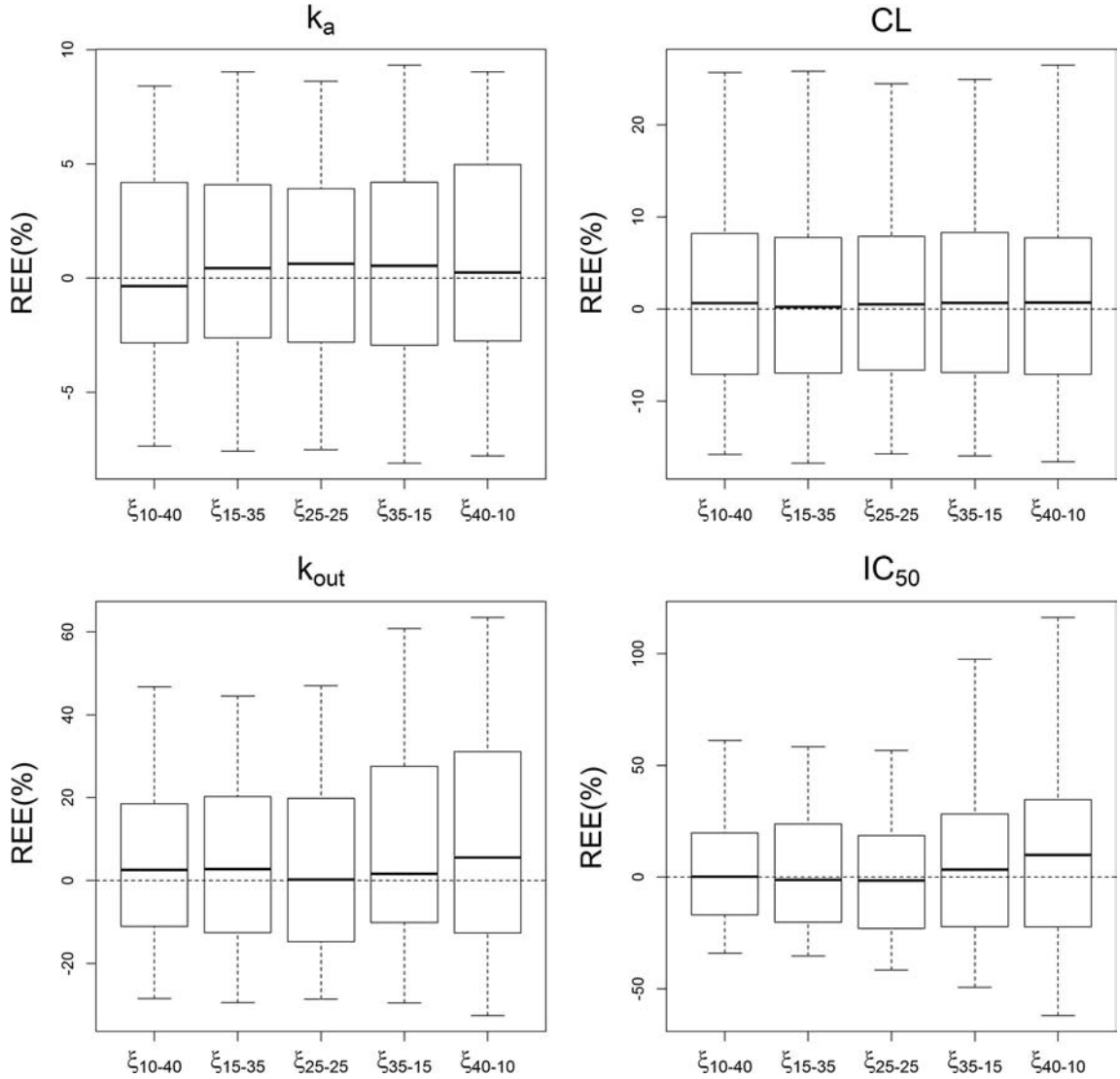

Fig. 5 Boxplot of relative estimation error (REE) for PK parameters k_a and CL (*top panel*) and PD parameters k_{out} and IC_{50} (*bottom panel*) in various two-stage adaptive designs.

fact of having used a small number of simulated dataset after the first stage, which was due to software connection limitation that comported manual work to import estimated parameters after first cohort needed for the optimisation of the design of the second stage. The need of additional studies to provide further validation of the approach was therefore necessary.

In the present study, we compared by clinical trial simulation various adaptive designs for a PKPD model in oncology [12], where the model is defined by ordinary differential equation. Design optimisations were performed in PFIM 4.0 [10], thanks to the new features that allow for saving the FIM into a text file and using FIM as prior information for the evaluation or optimisation of a design. For each design we simulated 100 clinical trials and parameters were estimated after each cohort with MONOLIX 4.3. Parameter estimates were imported in R and iteratively used in PFIM through an R loop for design optimisation of the next cohort.

We first compared one-stage design and two-stage AD as confirmatory analysis of the previous work by Dumont *et al.* Although with the prior design ξ_0 based on wrong prior parameters, there is evident bias in PD parameters, estimation results with two-stage designs were close to those with the optimal design ξ_* and much better than those with ξ_0. Two-stage AD thus improved the design after the first stage and is therefore useful when the correct prior information is not available. We also compared various two-stage designs of different cohort size. The choice of two-stage designs with a small initial cohort is reasonable in some situation, for instance in early phases for ethical and safety reasons. Estimation results for designs with a large first cohort were less satisfactory compared with the other two-stage designs, because only few patients are then included in the second stage which is not enough to correct for the wrong initial design. In both Dumont *et al.* [23] and our study, results obtained with two-

Table III RRMSE % (and Standardized RRMSE with Respect to ξ_*) of Final Estimated Parameters in Balanced and Various Unbalanced Two-Stage Adaptive Designs (N = 50 Patients)

	RRMSE % (standardized RRMSE)				
Parameters	ξ_{10-40}	ξ_{15-35}	ξ_{25-25}	ξ_{35-15}	ξ_{40-10}
k_a (h^{-1})	5.5 (0.95)	5.5 (0.95)	5.0 (0.86)	5.3 (0.91)	5.6 (0.97)
V (L)	9.4 (0.95)	9.7 (0.98)	9.3 (0.94)	9.5 (0.96)	9.7 (0.98)
CL (L h^{-1})	12.4 (0.99)	12.5 (1.00)	12.5 (1.00)	12.5 (1.00)	12.5 (1.00)
ω^2_V	22.4 (0.98)	22.0 (0.96)	22.2 (0.97)	22.1 (0.97)	22.3 (0.98)
ω^2_{CL}	24.1 (0.98)	24.8 (1.01)	24.3 (0.99)	24.2 (0.98)	25.1 (1.02)
$\sigma_{slope,PK}$	10.6 (1.05)	10.0 (0.99)	9.9 (0.98)	9.9 (0.98)	9.9 (0.98)
k_{out} (h^{-1})	28.7 (1.21)	26.4 (1.11)	24.1 (1.01)	32.0 (1.34)	33.1 (1.39)
IC_{50} (mg L^{-1})	**49.1** (**2.22**)	36.0 (1.63)	30.3 (1.37)	**45.8** (**2.07**)	**57.2** (**2.59**)
$\omega^2_{k_{out}}$	60.5 (0.80)	63.8 (0.84)	60.9 (0.80)	58.8 (0.77)	62.9 (0.83)
$\omega^2_{IC_{50}}$	104.5 (1.45)	102.5 (1.42)	98.6 (1.37)	**197.6** (**2.74**)	**246.5** (**3.41**)
$\sigma_{inter,PD}$	6.2 (0.85)	6.7 (0.92)	6.2 (0.85)	6.4 (0.88)	6.4 (0.88)
Mean Standardized RRMSE	1.13	1.07	1.01	1.24	1.37

RRMSE in *bold* have at least a two-fold increase standardized RRMSE

stage designs were better than those obtained with ξ_0. Moreover, a balanced two-stage design, i.e., with same number of patients in the two cohorts, provided the smaller mean standardized RRMSE, and therefore was preferable within the different cohort sizes of two-stage designs. The present results confirmed the results obtained in Dumont *et al.* [23].

We then investigated adaptive designs with more stages, which, according to our knowledge, were never evaluated in NLMEM. We considered designs with a small number of patients in the first cohort ($N_1 = 10$). Results on RRMSEs were better in the three- and five-stage design considered, than in the two-stage design, but not much better than those obtained for the balanced two-stage design. Of note, the three-stage design that performed best, $\xi_{10-20-20}$, is again the balanced design of the remaining 40 patients after the first stage. More stage designs with larger size in the first cohort were not taken into account in this study. Further studies on feasibility of adaptive designs with more stage in clinical practice should be performed, especially if the prior guess is very far from the true value of parameters. But it should be noted that with more stages the practical implementation is more complex, hence two-stage AD seems a good approach [21].

There are several limitations in the scope of the simulation study performed here, limitations that were also present in [23]. First we assumed that the same elementary design was performed in patients belonging to the same cohort, with a fix number of sampling times. Second, we assumed that the

Table IV RRMSE % (and Standardized RRMSE with Respect to ξ_*) of Final Estimated Parameters in a Two-Stage Design, Two Three-Stage Designs and Five-Stage Design (N = 50 Patients). All Designs are Characterized by Having 10 Patients in the First Cohort

	RRMSE % (standardized RRMSE)			
Parameters	ξ_{10-40}	$\xi_{10-20-20}$	$\xi_{10-10-30}$	$\xi_{10-10-10-10-10}$
k_a (h^{-1})	5.5 (0.95)	5.6 (0.97)	5.6 (0.97)	5.5 (0.95)
V (L)	9.4 (0.95)	9.7 (0.98)	9.8 (0.99)	9.7 (0.98)
CL (L h^{-1})	12.4 (0.99)	12.5 (1.00)	12.4 (0.99)	12.4 (0.99)
ω^2_V	22.4 (0.98)	22.4 (0.98)	22.2 (0.97)	22.2 (0.97)
ω^2_{CL}	24.1 (0.98)	24.3 (0.99)	24.3 (0.99)	23.9 (0.97)
$\sigma_{slope,PK}$	10.6 (1.05)	10.7 (1.06)	10.7 (1.06)	10.8 (1.07)
k_{out} (h^{-1})	28.7 (1.21)	22.3 (0.94)	25.6 (1.08)	23.0 (0.97)
IC_{50} (mg L^{-1})	**49.1** (**2.22**)	27.1 (1.23)	31.8 (1.44)	26.3 (1.19)
$\omega^2_{k_{out}}$	60.5 (0.80)	65.8 (0.87)	72.4 (0.95)	73.0 (0.96)
$\omega^2_{IC_{50}}$	104.5 (1.45)	96.6 (1.34)	95.2 (1.32)	92.2 (1.28)
$\sigma_{inter,PD}$	6.2 (0.85)	6.5 (0.89)	6.5 (0.89)	6.4 (0.88)
Mean Standardized RRMSE	1.13	1.02	1.06	1.02

RRMSE in *bold* have at least a two-fold increase of standardized RRMSE

Table V Number of Different Elementary Design (n_ξ) and Number of Datasets When the Elementary Design is Equal to ξ_* (n_ξ^*), for the Various Stages, of the Two-, Three- and Five-Stage Studied Adaptive Designs

	2nd Stage		3rd Stage		4th Stage		5th Stage	
	n_ξ	n_ξ^*	n_ξ	n_ξ^*	n_ξ	n_ξ^*	n_ξ	n_ξ^*
Two-stage design								
ξ_{10-40}	12	24						
ξ_{15-35}	8	35						
ξ_{25-25}	6	49						
ξ_{35-15}	6	47						
ξ_{40-10}	6	45						
Three-stage design								
$\xi_{10-20-20}$	12	27	5	71				
$\xi_{10-10-30}$	12	28	6	61				
Five-stage design								
$\xi_{10-10-10-10-10}$	12	28	7	60	4	69	4	76

structural model was known, correct and similar for all the stages. As in early phases there usually is no certainty about the model whereas there are various possible models that can be considered, we suggest using a model averaging approach for future studies [27]. Third, we assumed that the dose was fixed and identical in all patients in all cohorts and that design optimisation was performed only on sampling times. It would be interesting to expand the approach also for dose findings, optimising for instance the maximum tolerated doses in addition to the sampling times.

In adaptive design, as in optimal design, it is also necessary to define at the beginning of the analysis some prior parameters values for the model, which are usually difficult to guess when correct information is not available. Prior parameters shown in Table I were assumed to be error free. Indeed D-optimality used here at each stage does not handle uncertainty in parameters. However it should be noted that here, the changes in prior and true parameters (four fold for CL and tenfold for k_{out}) do not intend to represent estimation uncertainty but are mimicking a change from preclinical to clinical parameters. In that case taking into account estimation uncertainty using a robust design criteria, for instance for the first cohort, is expected to make only few changes. Further studies are needed to analyze the impact of the use of robust criteria in adaptive designs. Furthermore, to introduce this uncertainty in the parameters, several robust designs criteria were developed for optimal designs of fixed experiments in previous studies [17, 28, 29]. The common characteristic that links these methods is the assumption of assigning prior distributions for the parameters, rather than constraining them to a fixed value. A perspective of this work could thus be to use a robust design approach for defining prior information in the first stage of adaptive design.

In this work, we only changed two parameters, one in the PK model (CL) and one in the PD model (k_{out}) and we made rather large change in order to clearly see a variation of the shape of PK and PD curves with respect to time. In addition, by changing IC_{50} to four fold bigger or smaller, the optimal PD design did not change. When reducing inter-individual variability on PK parameters (30% instead of 70%), the design ξ_* was only slightly changed for PK (0.1, 1.5, 12 h), whereas ξ_0 was unchanged. The full simulation study with that lower variability was not performed. Inter-patient variability on k_a was not considered in the present study.

To conclude, two-stage designs provided satisfactory results close to those of the design optimised with true parameters, which allowed compensating the poor information of the prior design. The balanced two-stage design seems the best option, as in Dumont *et al.* [23], although a two responses (PKPD) model in oncology was used. Furthermore, in case of small first cohort, more adaptations may be performed but those designs are more complex to implement in clinical practice.

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