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Evaluation of the Fisher information matrix in nonlinear mixed effect models using adaptive Gaussian quadrature

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ABSTRACT

Nonlinear mixed effect models (NLMEM) are used in model-based drug development to analyse longitudinal data. To design these studies, the use of the expected Fisher information matrix (M_F) is a good alternative to clinical trial simulation. Presently, M_F in NLMEM is mostly evaluated with first-order linearisation. The adequacy of this approximation is, however, influenced by model nonlinearity. Alternatives for the evaluation of M_F without linearisation are proposed, based on Gaussian quadratures. The M_F, expressed as the expectation of the derivatives of the log-likelihood, can be obtained by stochastic integration. The likelihood for each simulated vector of observations is approximated by Gaussian quadrature centred at 0 (standard quadrature) or at the simulated random effects (adaptive quadrature). These approaches have been implemented in R. Their relevance was compared with clinical trial simulation and linearisation, using dose–response models, with various nonlinearity levels and different number of doses per patient. When the nonlinearity was mild, three approaches based on M_F gave correct predictions of standard errors, when compared with the simulation. When the nonlinearity increased, linearisation correctly predicted standard errors of fixed effects, but over-predicted, with sparse designs, standard errors of some variability terms. Meanwhile, quadrature approaches gave correct predictions of standard errors overall, but standard Gaussian quadrature was very time-consuming when there were more than two random effects. To conclude, adaptive Gaussian quadrature is a relevant alternative for the evaluation of M_F for models with stronger nonlinearity, while being more computationally efficient than standard quadrature.

1. Introduction

Nonlinear mixed effect models (NLMEM) are frequently used in model-based drug development to analyse longitudinal data obtained during clinical trials (Lalonde et al., 2007; Smith and Vincent, 2010). They were introduced about 40 years ago (Sheiner et al., 1972, 1977) and were initially used in pharmacokinetic analyses as an alternative to the non-compartmental approach (NCA) (Gabrielson and Weiner, 2006). This modelling approach is more complex than NCA, but allows for the analysis of few samples per subject. It accounts for within and between subject variability, and is appropriate for exploiting the richness of repeated measurements. Consequently, this approach is increasingly used in the biomedical field, not only for pharmacokinetic analyses (Sheiner et al., 1972, 1977), but also for analyses of viral loads (Perelson and Ribeiro, 2008), of bacterial resistance to antibiotics (Nielsen et al., 2007), and of the dose–response relationship. This

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approach has become the main statistical tool in pharmacometrics, the science of quantitative pharmacology (Vander Graaf, 2012). Parameters of these models are commonly estimated by likelihood maximisation (Dartois et al., 2007). However, the nonlinearity of the structural model prevents a closed form solution for the integration over the random effects in the expression of the likelihood function. Many approaches have been proposed over the years to overcome this difficulty, and implemented in several estimation software packages. These are first-order marginal quasi-likelihood or first-order linearisation (Lindstrom and Bates, 1990) in NONMEM, R, Splus, Laplace approximation (Wolfinger, 1993) in NONMEM and SAS, adaptive Gaussian quadrature (Pinheiro and Bates, 1995) in SAS and in the R package `lme4`, Stochastic Approximation Expectation Maximisation (SAEM) (Kuhn and Lavielle, 2005) in MONOLIX and NONMEM. Pillai et al. (2005) described these estimation methods in a review paper and recently, Plan et al. (2012) compared their performance, showing that adaptive Gaussian quadrature, although the slowest, was generally the best method.

Before the modelling step to estimate parameters, it is important to define an appropriate design, which consists in determining a balance between the number of subjects and the number of samples per subject, as well as the allocation of times and doses, according to experimental conditions. The choice of design is crucial for an efficient estimation of model parameters (Al-Banna et al., 1990; Hashimoto and Sheiner, 1991; Jonsson et al., 1996), especially when the studies are conducted in children or in patients where only a few samples can be taken per subject. The main approach for design evaluation has long been based on clinical trial simulation (CTS), but it is a cumbersome method and so the number of designs that can be evaluated is limited. An alternative approach has been described in the general theory of optimum experimental design used for classical nonlinear models (Atkinson et al., 2007; Walter and Pronzato, 2007; Atkinson et al., 2014), relying on the Rao–Cramer 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 estimate of the parameters and its diagonal elements are the expected variances of the parameters. Several criteria based on M_F have been developed to evaluate designs. One of the criteria widely used is the criterion of D-optimality, which consists in maximising the determinant of M_F. The computation of this criterion requires a priori knowledge of the model and its parameters, which can usually be obtained from previous experiments. This leads to the concept of "locally optimal designs", which has been studied in several publications (Chernoff, 1953; Box and Lucas, 1959; D'Argenio, 1981). Since there is no closed form of the likelihood in NLMEM, there is no analytical expression of M_F. An approximation of the expected M_F has been proposed for NLMEM, using first order linearisation of the model around the random effect expectation (Mentré et al., 1997; Retout et al., 2002; Bazzoli et al., 2009). This approach has been implemented in several software programs (Bazzoli et al., 2010; Leonov and Aliev, 2012; Gueorguieva et al., 2007; Nyberg et al., 2012) such as PFIM (INSERM, University Paris Diderot), POPED (University of Uppsala), POPDES (University of Manchester), and POPT (University of Otago), frequently used to design new studies in academia as well as in pharmaceutical companies (Mentré et al., 2013).

However, it has been shown that the use of the linearisation (LIN) approach is only appropriate if the variances of the random effects are small, or the nonlinearity is mild (Jones and Wang, 1999; Jones et al., 1999). Consequently, as pointed out by Han and Chaloner (2005), when an optimal design is found using this approximation but the estimation is carried out using a true NLMEM, the performance of the design needs further investigation. The nonlinearity of a model with respect to its parameters is defined from the behaviour of the first order derivatives of the model function. Its consequences on the structural identifiability of a model have been studied by Walter and Pronzato (1995). The notion of level of nonlinearity ("mild" or "strong" as mentioned in this paper) is derived from the term "close to linear" introduced when evaluating a nonlinear model's behaviour (Fletcher and Powell, 1963). Measures of nonlinearity have been studied in several publications (Bates and Watts, 1980; Cook and Goldberg, 1986; Smyth, 2002) in order to evaluate whether the "close to linear" condition is satisfied and to indicate if the linear approximation is reasonable or questionable. When first-order linearisation is to be avoided, alternative approaches are necessary. Various new approaches have been proposed, but these are not always better than the usual first-order linearisation. For instance, linearisation of the model around the individual values of the random effects (Retout and Mentré, 2003) or around the expected mode of the marginal likelihood (Nyberg et al., 2012) has been proposed but is quite time consuming because Monte Carlo simulations are needed. Other approaches based on the Laplace approximation (Vong et al., 2012) or Monte Carlo integration (Mielke, 2012) give correct predictions for the precision of parameter estimation, but they are also very time consuming. Another possible alternative for computing the Fisher information matrix in designing studies is the use of Gaussian quadrature rules. This consists in approximating integrals of functions with respect to a given probability density by a weighted sum of function values at abscissas chosen within the integration domain. It has been shown that adaptive Gaussian quadrature (AGQ) performs better than standard Gaussian quadrature (GQ) in estimation (Pinheiro and Bates, 1995); the difference between the two approaches is that the grid of nodes is centred at the expectation of the random effects in GQ while it is centred at the conditional modes of the random effects in AGQ. Neither approach has ever been proposed for designing studies with different types of models, except in an example of an HIV dynamic model written with ordinary differential equations (Guedj et al., 2007).

In this context, we aim to propose alternatives to linearisation for evaluating the predicted Fisher information matrix, based on GQ and AGQ. In order to challenge and investigate the performance of both new approaches as well as linearisation compared with CTS, we use examples of dose–response trials inspired by the article of Plan et al. (2012) comparing different estimation methods. Dose–response studies are of critical importance in drug development and need to be planned carefully (Bretz et al., 2010; Pronzato, 2010; McGree et al., 2012) but little has been done to study their design in the context of NLMEM. We consider the sigmoid $E_{\max}$ model, with various degrees of nonlinearity (i.e. different sigmoidicity coefficients), and in addition a linear model where M_F can be calculated exactly.