Abstract Generalized linear and nonlinear mixed-effects models are used extensively in biomedical, social, and agricultural sciences. The statistical analysis of these models is based on the asymptotic properties of the maximum likelihood estimator. However, it is usually assumed that the maximum likelihood estimator is consistent, without providing a proof. A rigorous proof of the consistency by verifying conditions from existing results can be very difficult due to the integrated likelihood. In this paper, we present some easily verifiable conditions for the strong consistency of the maximum likelihood estimator in generalized linear and nonlinear mixed-effects models. Based on this result, we prove that the maximum likelihood estimator is consistent for some frequently used models such as mixed-effects logistic regression models and growth curve models.

Keywords Maximum likelihood estimator · Generalized linear mixed-effects models · Nonlinear mixed-effects models · Random effects · Strong consistency

AMS subject Classification: Primary 62F12, secondary 62J02

1 Introduction

Since the work of Sheiner and Beal (1980), generalized linear and nonlinear mixed-effects models have been used extensively in biomedical, social, and agricultural sciences. In the literature, two categories of nonlinear mixed-effects models have been used to model repeated measurement and longitudinal data. The first is the
generalized linear mixed-effects model and the second is the (Gaussian based) nonlinear mixed-effects model. In order to establish results which can be applied to both models, we consider a general model which is described as follows.

Consider the data partitioned into \( n \) clusters (or subjects), where the \( i \)th cluster (or subject) consists of \( p_i \) observations,

\[
y_i = (y_{i1}, \ldots, y_{ipi})^T.
\]

The model for the data is described in two stages. In the first stage, given a random variable \( b_i = (b_{i1}, \ldots, b_{iv})^T \), the conditional probability density function of \( y_i \) is

\[
\pi_i(y_i, \tau, b_i),
\]

where \( \tau \) is a vector of \( u \) unknown fixed-effect parameters. We also assume that \( y_1, \ldots, y_n \) are conditionally independent. In the second stage, the unobservable random-effect vectors \( b_1, \ldots, b_n \) are assumed to be a random sample from a distribution with probability density function \( \phi(b_i, \theta) \). Here \( \theta = (\theta_1, \ldots, \theta_w) \) is a vector of \( w \) unknown structural parameters. Let \( \Omega \) denote the parameter space for \((\tau, \theta)\). We are interested in estimating \((\tau, \theta)\) in \( \Omega \), based on the observations \( y_1, \ldots, y_n \).

When \( \pi_i(y_i, \tau, b_i) \)’s belong to the exponential family for given random variable \( b_i = (b_{i1}, \ldots, b_{iv})^T \), then this model reduces to the generalized linear mixed-effects model; when \( \pi_i(y_i, \tau, b_i) \)’s and \( \phi(b_i, \theta) \) are the density functions of normal distributions, then this model reduces to the (Gaussian based) linear mixed-effects model.

Models of this type arise in longitudinal studies, repeated measurement experiments over time and space and various other experiments that yield correlated multivariate data. The areas of application include biomedical, social, and agricultural sciences. Specific examples will be provided in the Introduction and in the Application section. Anderson and Aitkin (1985) suggested a logistics mixed-effects model to analyze interviewer variability. Davidian and Giltinan (1993) gave two examples of Gaussian based nonlinear mixed-effects models for biomedical and biological problems. Other examples in pharmacokinetics, clinical trials, and epidemiology are available in Tutz and Fahrmeir (2001), Davidian and Giltinan (1995), Mentré and Gomeli (1995), Pinheiro and Bates (1995), Roe (1997), Vonesh and Chinchilli (1997), Wolfinger and Lin (1997) and Vonesh et al. (2002).

MLE is used to make inference for the unknown parameters. Obtaining MLE’s involves tremendous computational difficulty because of the integrated likelihood, which does not have a close form. MLE is currently computed via several different approaches. These approaches include numerical integration techniques (e.g., Hedeker and Gibbons 1994; Pinheiro and Bates 1995) and Markov Chain Monte Carlo techniques (e.g., Zeger and Karim 1991; McCulloch 1997; Booth and Hobert 1999). Other than MLE, some other approaches have also been suggested in literature. Jiang (1999) considered a robust conditional inference approach about generalized linear mixed-effects models. Liang and Zeger (1986) proposed generalized estimating equation approach (GEE), which is a marginal approach to repeated measurements and longitudinal data analysis. Readers are referred to Davidian and Giltinan (1995), Vonesh and Chinchilli (1997), Tutz and Fahrmeir (2001), Diggle et al. (2002), and McCulloch (2003), and references therein for more information.