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Efficient hybrid EM for linear and nonlinear mixed effects models with censored response

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Abstract

Medical laboratory data are often censored, due to limitations of the measuring technology. For pharmacokinetics measurements and dilution-based assays, for example, there is a lower quantification limit, which depends on the type of assay used. The concentration of HIV particles in the plasma is subject to both lower and upper quantification limit. Linear and nonlinear mixed effects models, which are often used in these types of medical applications, need to be able to deal with such data issues. In this paper we discuss a hybrid Monte Carlo and numerical integration EM algorithm for computing the maximum likelihood estimates for linear and non-linear mixed models with censored data. Our implementation uses an efficient block-sampling scheme, automated monitoring of convergence, and dimension reduction based on the QR decomposition. For clusters with up to two censored observations numerical integration is used instead of Monte Carlo simulation. These improvements lead to a several-fold reduction in computation time. We illustrate the algorithm using data from an HIV/AIDS trial. The Monte Carlo EM is evaluated and compared with existing methods via a simulation study.

Keywords: Monte Carlo EM; HIV-1 viral dynamics; Quantification limit; LME; NLME; Likelihood estimation

1. Introduction

When analyzing medical data, the statistician is often confronted with censored observations. For laboratory data, these may be due to limitations of the measuring technology. In pharmacokinetics the concentration of drug in plasma is subject to a limit of quantification below which the measurement is not reliable, or even possible. Similarly, the HIV-1 viral load, which is currently the primary marker of HIV infection, has a lower and a upper quantification limit (QL), which depend on the type of assay used. The viral load of patients receiving anti-retroviral treatment will typically decline and stay for a longer period of time below the lower limit of quantification.

Since in biomedical applications the observations are often non-linear and longitudinal, non-linear mixed effects models (NLME) are a popular modelling tool for these data. In practice, the censoring problem is ignored, or dealt with in an ad hoc way. In this paper we use some novel EM computational techniques in order to adjust for censored responses

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in NLME estimation. The E-step uses numerical integration, for clusters with up to two censored observations, or Monte Carlo integration for clusters with more than two censored observations. As such our algorithm is a hybrid between Monte Carlo EM (MCEM) and a "classical" EM using numeric integration. We call it a hybrid EM (HEM). In this algorithm the data augmentation scheme involves both the random effects and the censored observations. An alternative computational method is multiple imputation (Rubin, 1996; Fitzgerald et al., 2002, MI). While HEM has the potential of more precise estimation of the MLE for censored data, MI enjoys straightforward implementation using existing NLME software, such as the `nlme` suite for R/S-plus (Pinheiro and Bates, 2000), or PROC NLMIXED in SAS (Wolfinger, 1999). We compare the two methods and show here that both methods are superior to ad hoc approaches, such as using the censoring limits as observed values. The end user has the ultimate choice in the trade-off between precision and ease of implementation. This choice has been heavily influenced by the absence of ready-to-use software for NLME with censored response, although Hughes (1999) also made available software for linear mixed-effects (LME) models with censored response. For those choosing HEM we provide a versatile, self-monitoring and computationally efficient program implemented in R. The improvements with respect to the "state of the art" include: automatic monitoring of convergence based on an approximate likelihood objective function; automatic choice of Monte Carlo sample size; block-sampling of the censored data and random effects; efficient computation using dimension reduction using QR decomposition; incorporating the linearization step in the EM loop. In addition, we applied the same improvements to an algorithm for LME with censored response.

We illustrate the general methodology developed here to the analysis of an AIDS clinical trial. In ACTG 315 study (Lederman et al., 1998) the viral dynamics are nonlinear, and later viral load observations are often below the limit of quantification of the assay (left-censored). A second situation (analysis not presented) regards modelling the setpoint HIV-1 RNA levels of untreated individuals with acute HIV infection from the Acute Infection and Early Disease Research (AIEDRP) study. Here observations taken in the acute stage of infection are often *above* the limit of quantification of the assay (right censored).

The likelihood of NLME models with completely observed response is untractable, and the MLE is not available in closed form. Briefly stated, NLME are solved by iteratively linearizing the mean function using a Taylor expansion, followed by a LME step (Laird and Ware, 1982; Lindstrom and Bates, 1990). Several linearization methods have been proposed: Sheiner and Beal (1980), Lindstrom and Bates (1990), Wolfinger (1993), Kiuchi et al. (1995), Pinheiro and Bates (1995). In each case the resulting solution is an approximate MLE. Pinheiro and Bates (1995) concluded based on a comparative study that the method of Lindstrom and Bates (1990) using iterative linearization around the current estimates for the parameter and random effects estimates performs well. For a detailed account of the NLME see the recent monographs of Davidian and Giltinan (1995), Vonesh and Chinchilli (1997), and Pinheiro and Bates (2000). The issue of censored response for a LME was considered by Hughes (1999), who used a MCEM algorithm extending the methods of Laird and Ware (1982). For NLME our work builds on Fitzgerald (2000). Wu (2002, 2004) has extended the work of Hughes (1999) to LME and NLME which also accommodate error in variables. Beal (2001) discusses practical issues related to left-censored observations in pharmacokinetics and compares several methods for dealing with them in fixed-effects modelling.

2. MCEM for LME models with censored response

After briefly summarizing Hughes' MCEM algorithm for LME, we describe our computationally efficient implementation, including a simple and general framework for automatic selection of Monte Carlo sample size and monitoring convergence of the HEM. This forms the basis for the algorithm for NLME with censored response, presented in the next section.

2.1. Hughes' algorithm

Hughes (1999) proposed a MCEM algorithm for LME with censored data. Consider the Laird–Ware LME model

$$y_i = X_i\beta + Z_i b_i + e_i, \tag{1}$$

$i = 1, \ldots, m$ with b_i and $e_i = (e_{i1}, \ldots, e_{in_i})^\top$ given by

$$b_i \overset{iid}{\sim} N(0, \sigma^2 D), \quad e_{ij} \overset{iid}{\sim} N(0, \sigma^2), \tag{2}$$