Proposition de communication pour les journées 2017 du GDR « Statistique et Santé »
et de la Société Française de Biométrie

Using Hamiltonian Monte-Carlo to design longitudinal studies with discrete outcomes accounting for model and parameter uncertainties

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Introduction: Nonlinear mixed effect models (NLMEMs) are widely used for the analysis of longitudinal data. To design these studies, the expected Fisher Information Matrix (FIM) can be used instead of performing time-consuming clinical trial simulations (CTS) [1]. A method evaluating the FIM, without any linearization, based on Monte-Carlo and Hamiltonian Monte-Carlo (MC/HMC), has been proposed and implemented in the R package MIXFIM [2]. This method uses Stan [3], which efficiently draws HMC samples and calculates partial derivatives of the log-likelihood, and has been shown to perform well with both continuous and discrete data [2]. However, it requires a priori knowledge of models and parameters, which lead to designs that are locally optimal. We aimed to propose and evaluate a new approach based on MC/HMC for robust optimal designs in longitudinal studies taking into account model and parameter uncertainties. We illustrated this approach in design optimization for repeated binary and count data.

Methods: To determine informative designs given the model and population parameter values, different optimality criteria based on the FIM evaluated by MC/HMC can be computed, according to different purposes [4]: the D-optimality (i.e. maximizing the determinant of the FIM) to optimize the precision of the whole set of population parameters, the Ds-optimality to accommodate situations in which only a subset of the model parameters is of interest (e.g. covariate effects), and the DDs-optimality to find a compromise between the D- and Ds-optimality. Then, uncertainty in model, given population parameter values, is taken into account using the compound D-optimality (or Ds and DDs) to propose a common informative design by averaging over a set of candidate models [5,6].

To account for parameter uncertainty for a given model, we evaluated the robust FIM as the expectation of the FIM, using MC/HMC, over the distribution of population parameters and computed the DE-criterion as the determinant of the robust FIM. Then, the compound DE-optimality was used to find a design which was robust with respect to both model and parameters.

Illustrations/Results: These methods were illustrated in two examples of longitudinal discrete studies. The first example involved a logistic model for binary responses over time in two treatment groups. Combinatorial optimization is performed to determine the optimal location of a limited number of sampling times common to four candidate models. Using the expected FIM, we also predicted the number of subjects needed to detect a treatment effect in all the four models. The performance of the chosen design was evaluated by CTS in terms of precision for parameter estimation and power of the Wald test to detect a treatment effect.

The second example involved a Poisson model for count responses across several doses. We assumed a log-normal a priori distribution characterizing the uncertainty in the population parameter values as well as five candidate models describing the relationship between the logarithm of the event rate parameter and the dose. We performed combinatorial optimization of two doses in addition to the dose 0 (i.e. placebo).

We found that assuming uncertainty in model and parameters could lead to different optimal designs, and misspecification of models could lead to designs with low efficiencies. In the binary example, the compound DDs-optimal design is efficient across four candidate models and allow a compromise between the overall precision of estimation and the power of test. The estimation error and the power predicted using the expected FIM for the proposed design are close to the values obtained by CTS. In the count example, the compound DE-optimality provided a design which was informative for the five candidate models and robust with respected to population parameter values.

Conclusions: The proposed design strategy based on MC/HMC and compound optimality theory is a relevant approach which enabled, for the first time, optimization of sparse designs for longitudinal discrete data accounting for model and parameter uncertainties.

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