Using Hamiltonian Monte-Carlo to design longitudinal count studies accounting for parameter and model uncertainties

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Abstract

Nonlinear mixed effect models (NLMEMs) are widely used for the analysis of longitudinal data. To design these studies, optimal designs based on the expected Fisher information matrix (FIM) can be used. A method evaluating the FIM, without any linearization, based on Monte-Carlo Hamiltonian Monte-Carlo (MC-HMC) has been proposed and implemented in the R package MIXFIM [1] using Stan [2], which efficiently draws HMC samples and calculates partial derivatives of the log-likelihood. This approach, however, requires a priori knowledge of models and parameters, which leads to designs that are locally optimal. The objective of this work was to extend this MC-HMC-based method to evaluate the FIM in NLMEMs accounting for uncertainty in parameters and in models, and to apply the proposed approach to repeated count data.

When introducing uncertainty in the population parameters, we evaluated the robust FIM as the expectation of the FIM computed by MC-HMC for the population parameters. Then, the compound D-optimality criterion [3, 4] was used to find a common CD-optimal design for several candidate models. A compound DE-criterion was used to find the CDE-optimal design which was robust with respect to both parameters and model. These methods were applied in a longitudinal Poisson count model where the event rate parameter is a function of the dose level. We assumed a log-normal a priori distribution characterizing the uncertainty in the population parameter values as well as several candidate models describing the relationship between the logarithm of the event rate parameter and the dose level. We performed combinatorial optimization of two doses. Assuming uncertainty in parameters led to different optimal designs, and misspecification of models led to designs with low efficiencies. The CD- or CDE-optimal designs provided a good compromise for different candidate models.

In conclusion, MC-HMC is a relevant approach allowing for the first optimization of designs for repeated discrete data accounting for uncertainty in parameters and in candidate models.

References:

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