Handling Underlying Discrete Variables with Mixed Hidden Markov Models in NONMEM

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Objectives: Unobserved phenomena/covariates are commonly not included in models, though many may be of great importance, hence ignoring them may cause a bias in estimates, e.g., masking effect of rescue medication in pain trials. Besides, latent variable models that represent the underlying disease have become an interest, due to their attractive drug effect characterization properties. Mixed Hidden Markov models (MHMM), capable of handling Markov chains of unobserved states and previously proposed [1], require maximum likelihood estimation (MLE) computation summing over all previous conditions.

The objectives of this work were to explore various MHMM implementations in NONMEM and to expand the investigation of the benefits of this methodology.

Methods: MHMM methodology was implemented in NONMEM7.3 with an initial stationary distribution and a scaling of the forward probabilities. A subroutine involving the Viterbi algorithm was used to evaluate the most likely hidden states chain during post-hoc analysis.

First, 100 copies of a hypothetical trial (60 HIV+ patients randomized to placebo or treatment with 60 observations each) were simulated and re-estimated with different models and MLE methods. Second, an extension to a multivariate MHMM was developed (2 theoretical types of COPD records -1 measurement, 1 patient reported outcome- linked to presence or absence of relapse).

Results: MHMM can be implemented in NONMEM for systems involving 2 or more hidden states, discrete or continuous “open” observations and 1 or multiple variables. EM-methods, when applied to MHMMs, seem to be equally or more precise and accurate for fixed –not random– effects as well as faster than Laplace. In the 2 examples, MHMMs led to higher power to detect a drug effect, which was estimated closer to its true value compared to non-Markovian model (NMM).

Conclusions: MHMM offer possibilities of better understanding and modeling of underlying data in numerous applications.


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