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 ➔ ignoring may cause bias in estimates, e.g., masking effect of rescue medication in pain trials.
- Latent variable models have attractive properties, several types have recently been presented*, .e.g., mixed hidden Markov models (MHMM) ➔ studying their properties further is of interest.
- The aims of this work were to explore various MHMM implementations in NONMEM and to expand the investigation of the benefits of this methodology.

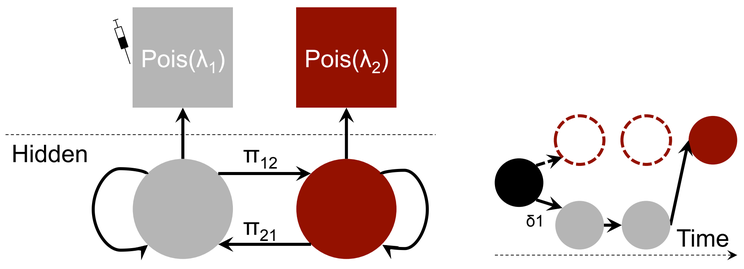
Methods

Implementation:

- Sets of 100 stochastic simulations and estimations (SSE) in NONMEM 7.3.
- Simulations involved randomly attributing stationary distributions (δ) and subsequently applying transitions (π) according to a Markov model.
- Estimations used the Forward algorithm, summing over all the probabilities of each state at each position. Post-hoc subroutine used the Viterbi algorithm, in order to evaluate the most likely hidden states chain.

Model and data I:

- Simulation model components: 2 hidden states, e.g., concomitant infection absent or present, and 2 “open” Poisson distributions, e.g., CD4 counts. Drug effect (DE): disease modifying as additive on mean count (λ) slope (TE).
- Study design: 60 individuals, e.g., HIV+ patients, randomized to placebo or treatment and followed over 60 time points, e.g., monthly during 5 years.



$$\pi_{12_i} = 1 \Big/ \left(1 + e^{-\left(Logit(\pi_{12}) + \eta_{12_i} + TE_{\pi_i} \cdot t_i\right)}\right)$$

$$\pi_{21_i} = 1 \Big/ \left(1 + e^{-\left(Logit(\pi_{21}) + \eta_{21_i}\right)}\right)$$

$$\lambda_{1_i} = \theta_1 \cdot e^{\eta_{1_i}} - \left(TE_{\lambda_i} - DE\right) \cdot t_i$$

$$\lambda_{2_i} = \lambda_1 - \theta_2 \cdot e^{\eta_{2_i}}$$

Figure 1: Schematic representation of a MHMM structure and the start of a time series, with equations of Model I.

Investigation of estimation methods:

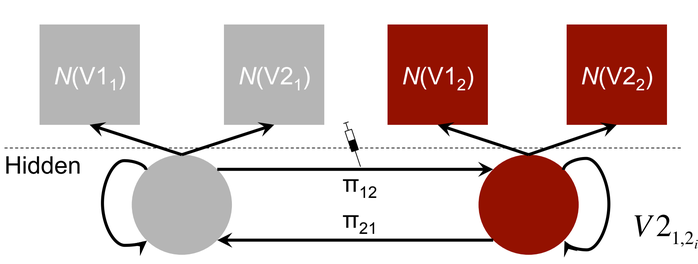
- Estimation of data I using Laplace (`METHOD=1 LAPLACE -2LL PRINT=1 MAXEVAL=9999 NOHABORT NOINTER NUMERICAL SLOW OPTMAP=1 ETADER=3`), Importance Sampling (`METHOD=IMP LAPLACE -2LL PRINT=1 NITER=30 NOINTER NOHABORT SIGL=8 RANMETHOD=P MAPITER=0`) and SAEM (`METHOD=SAEM LAPLACE -2LL NBURN=300 NITER=300 CTYPE=3 PRINT=10 NOINTER NOHABORT SIGL=8 RANMETHOD=P`).

Exploration of benefits:

- Estimation (SAEM) of data I with simulation model (MHMM) and non-Markovian model (NMM) consisting in 1 Poisson distribution (with time and drug effect on λ).

Model and data II:

- Simulation model components: 2 hidden states, e.g., exacerbation absent or present, and 2x2 “open” continuous variables, e.g., FEV1 and PRO. Drug effect: on hidden transition as affects π_{12}, i.e., decreases probability of exacerbation.
- Study design: 30 individuals, e.g., COPD patients, randomized to placebo or treatment and followed over 60 time points, e.g., weekly during 15 months.



$$\pi_{12_i} = 1 \Big/ \left(1 + e^{-\left(Logit(\pi_{12}) + \eta_{12_i} + DE\right)}\right)$$

$$\pi_{21_i} = 1 \Big/ \left(1 + e^{-\left(Logit(\pi_{21}) + \eta_{21_i}\right)}\right)$$

$$V1_{1,2_i} = \theta_1 \cdot e^{\eta_{1_i}} + \varepsilon_{1_{ij}}$$

$$V2_{1,2_i} = \left(\theta_2 + \eta_{2_i}\right) \cdot \left(1 - T_{\max} \cdot (1 - e^{-\ln(2)/t_{1/2} \cdot t_i})\right) + \varepsilon_{2_{ij}}$$

Figure 2: Schematic representation of a MV-MHMM linked to two types of observations, with equations of Model II.

Exploration of extension:

- Estimation (SAEM) of data II with multivariate simulation model (MV-MHMM), MHMM (1 variable) and non-Markovian model (NMM) as continuous (V1).

Conclusions

- 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).
- MHMMs offer possibilities of better understanding and modeling underlying data in numerous applications.

Results

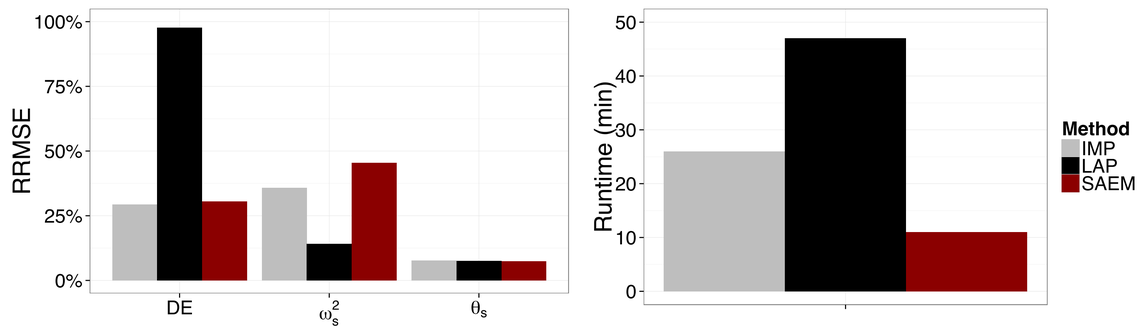


Figure 3: Mean relative RMSE for the drug effect (DE), the random effects (ω^2) and the fixed effects (θ) in Model I obtained with the three estimation methods investigated, as well as their associated mean runtimes.

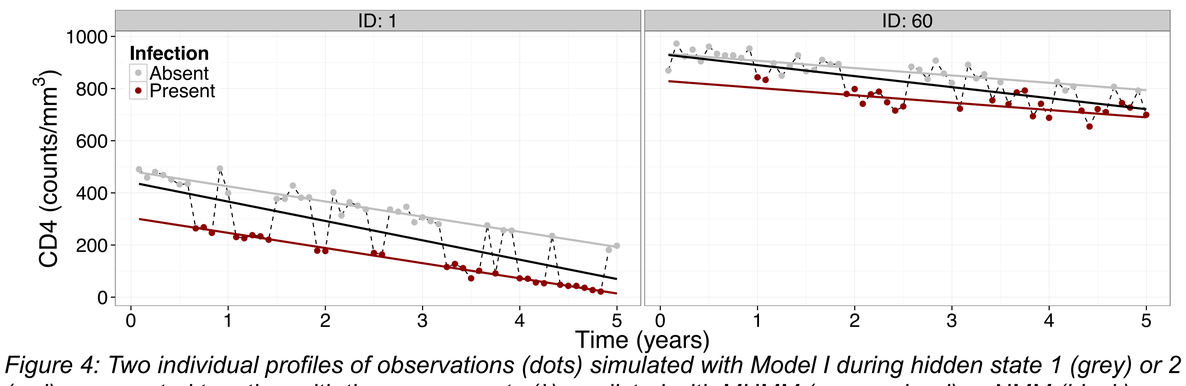


Figure 4: Two individual profiles of observations (dots) simulated with Model I during hidden state 1 (grey) or 2 (red) represented together with the mean counts (λ) predicted with MHMM (grey and red) or NMM (black).

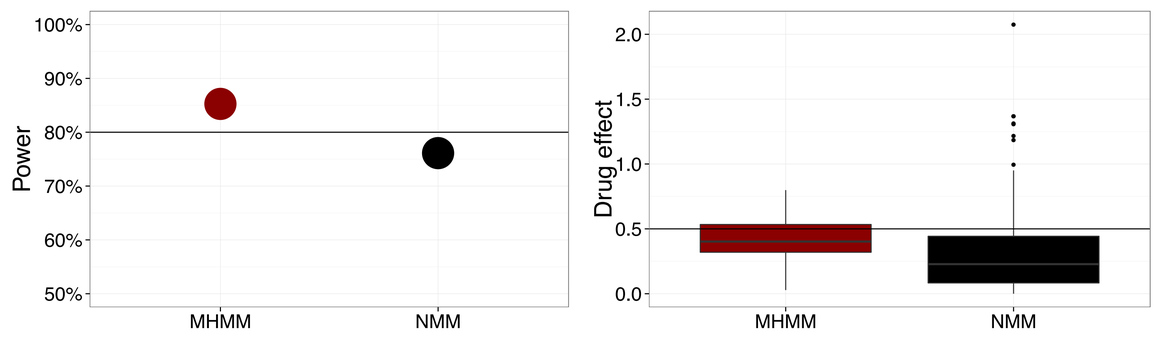


Figure 5: Power to detect the drug effect ($\Delta OFV > X^2(0.95)$) in data I with Model I (MHMM) and NMM and associated estimated values with the two models, when the true drug effect was 0.5 (horizontal line).

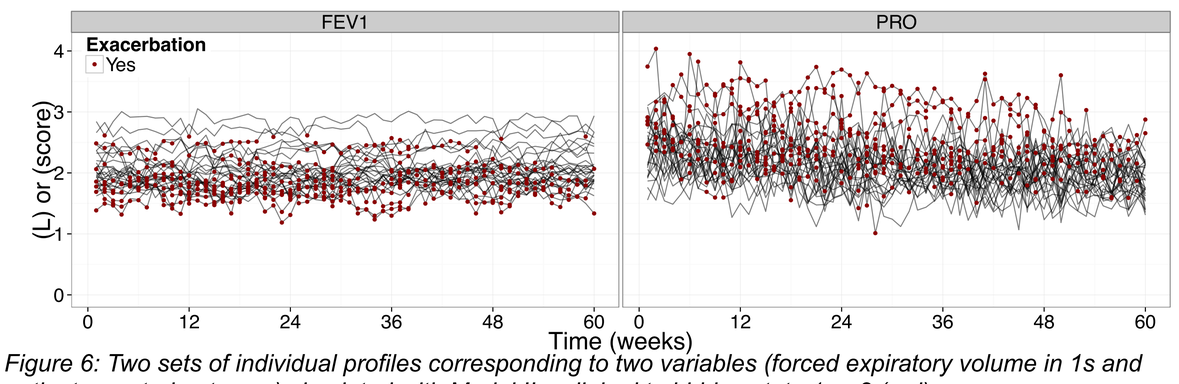


Figure 6: Two sets of individual profiles corresponding to two variables (forced expiratory volume in 1s and patient reported outcome) simulated with Model II as linked to hidden state 1 or 2 (red).

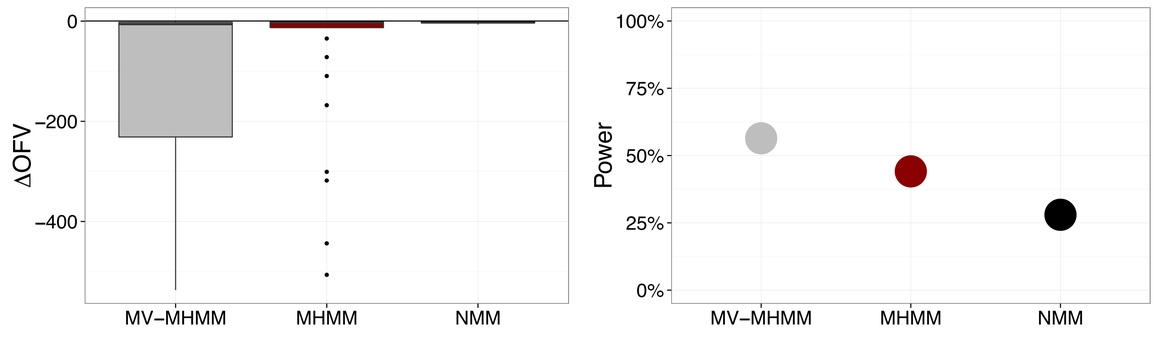


Figure 7: ΔOFV between full and reduced structures of estimation of data II with Model II (MV-MHMM), a MHMM linked to 1 variable and a NMM for 1 variable when detecting drug effect, with associated power.

Reference

* Delattre M, et al. Analysis of Exposure–response of CI-945 in Patients with Epilepsy: Application of Novel Mixed Hidden Markov Modeling Methodology. JPKPD (2012)

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