Parameter Estimation and Power Calculation with a Bivariate Mixed Hidden-Markov Model

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Introduction

Hidden-Markov models (HMMs) are a class of statistical models used to characterize relationships between observable and unobservable (hidden) stochastic processes. HMMs can be extended to include random effects (mixed hidden-Markov models (MHMMs) [1]) and to include multiple observation sources as multivariate MHMMs (MV-MHMM) [2], the latter allowing to take into account correlation between observations. The MV-MHMM may increase power over analyzing data only considering univariate observations.

Objectives

i) Extend univariate MHMMs presented by Plan. et al. [2] to a bivariate MHMM.

ii) Examine parameter estimation properties of MHMMs in NONMEM focusing on parameters related to hidden processes and correlation between observations.

iii) Determine the improvement in power to detect a hypothetical drug effect with a bivariate model compared with two univariate models.

Methods

Model and data

- BV-MHMMs simulations and estimations were performed in NONMEM 7.3 with the following components (Fig. 1): 2 hidden states related to disease activity (1 = non-active respiratory disease and 2 = active respiratory disease) and 2 measurements (FEV1 and a patient reported outcome [PRO] score) related through a bivariate normal distribution, including the correlation (ρ). A drug effect was included, decreasing the transition rate from state 1 to state 2, π_{12}. A time-constant model was used for FEV1, while PRO decreased over time. Inter-individual variability (IIV) was included on π_{12} and on FEV1 and PRO, separately in each state, reported as variance denoted as ω^2_{FEV1S2} where S1 represents state 1 (corresponding notation for PRO and state 2).

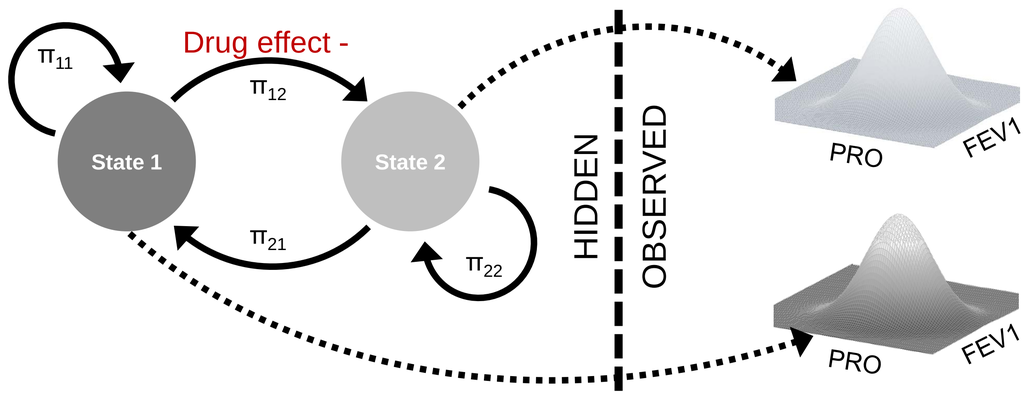

Figure 1: General bivariate MHMM structure. Random effects and covariates can be added on the hidden parameters such as π_{12} or on the observed processes.

- A large data set was simulated (n = 500), where half of the patients received the drug and half did not, and where each patient provided 60 weekly observations (equidistant and simultaneous) of each variable (FEV1 and PRO).

Parameter estimation with the MHMM

- Stochastic simulations and estimations (SSE) using PsN [3] were used to determine parameter uncertainty in the bivariate MHMM. Different model scenarios, with respect to parameter magnitude, were tested, where simulated data were estimated with correct models and purposely misspecified models e.g. simulated with ρ = 0.33 but estimated with ρ fixed to 0. The focus was on the hidden parameters π_{12} and π_{21}, the drug effect, and all IIV parameters.

Power to detect a drug effect

- Monte-Carlo mapped power (MCMP) [4] was used to determine the power of the bivariate model to detect a drug effect compared with a univariate model accepting only FEV1 or PRO observations in PsN. For the MCMP analysis the dataset was extended 10-fold (n = 5000) and a 5% significance level was chosen.

References:

[1] Altman RMK. Mixed Hidden Markov Models: An Extension of the Hidden Markov Model to the Longitudinal Data Setting. JASA. 2007.

[2] Plan E, et al. Handling Underlying Discrete variables with Mixed Hidden Markov Models in NONMEM. Poster presentation at PAGE. 2015.

[3] Keizer RJ, Karlsson MO, Hooker A. Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. CPT Pharmacometrics Syst Pharmaco. 2013, 2:e50.

[4] Vong C, Bergstrand M, Nyberg J, Karlsson MO. Rapid sample size calculations for a defined likelihood ratio test-based power in mixed effects models. 2012. AAPS J. Jun;14(2):176–86.

Conclusions

- ✓ A BV-MHMM was implemented in NONMEM allowing for simultaneous estimation of two observed stochastic processes and their correlations.
- ✓ Parameters related to hidden processes may be difficult to estimate depending on their magnitude. Estimation properties in MHMMs may need to be evaluated on a case-by-case basis.
- ✓ Power to detect a drug effect was higher when considering both variables in a BV-MHMM as compared to univariate models.

Results

Model and data

Bivariate FEV1 and PRO data obtained with the simulation model created in NONMEM are shown in Fig 2.

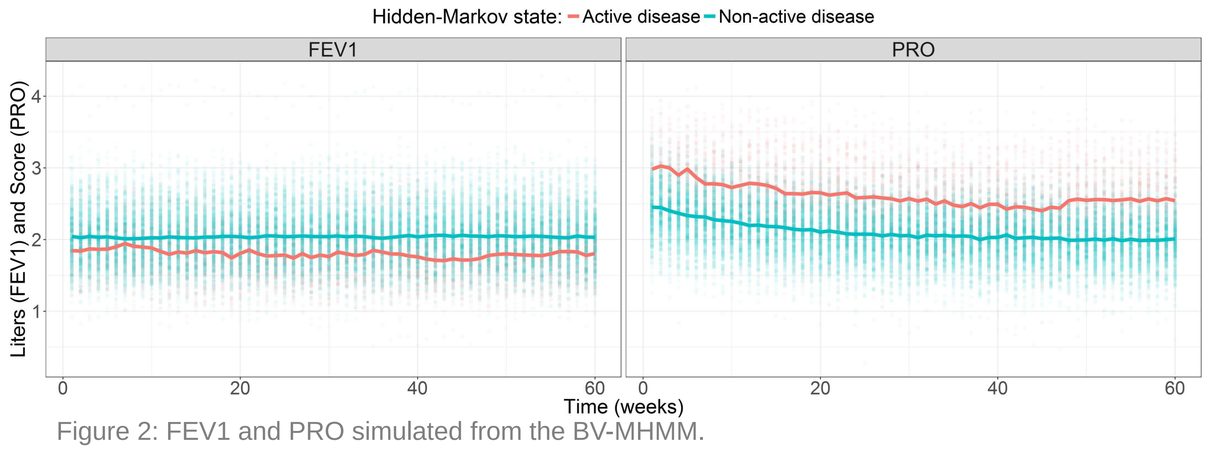

Figure 2: FEV1 and PRO simulated from the BV-MHMM.

Parameter estimation

Accuracy and precision in estimated parameters, given alternative model set-ups, are shown in Figs. 3A-B.

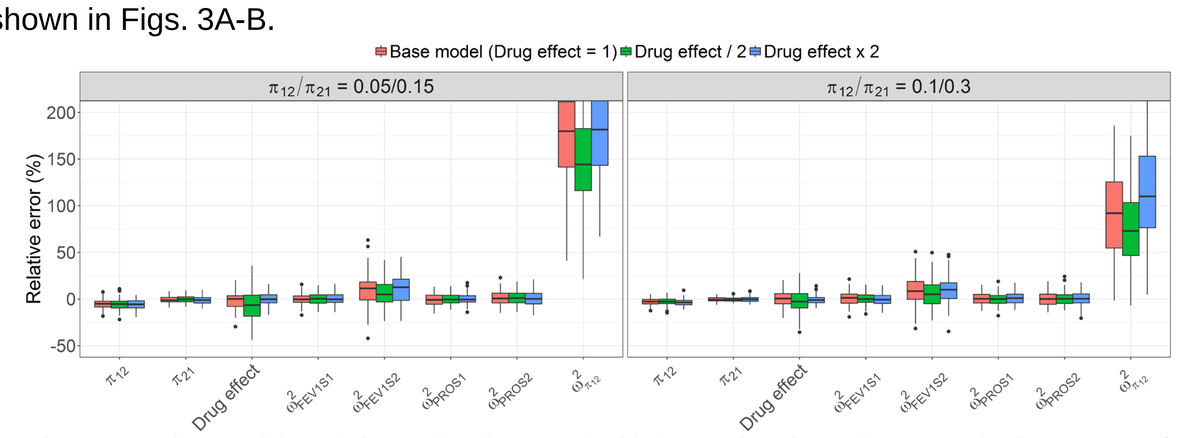

Figure 3A: The precision of drug effect improved with increasing drug effect magnitude. In general all parameters were more accurately estimated with an increase in transition probabilities. $\omega^2_{\pi 12}$ was in general poorly estimated, a result likely connected to the small number of transitions and presence of drug effect on π_{12}.

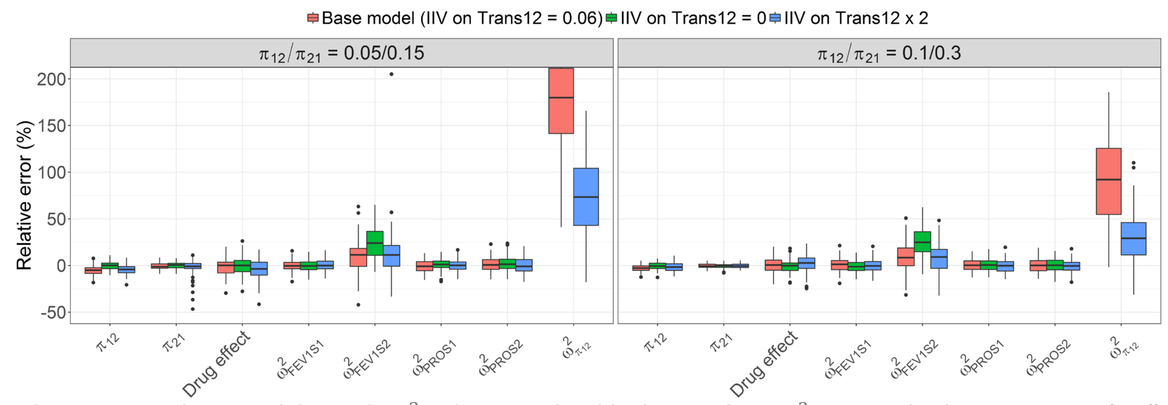

Figure 3B: The precision of $\omega^2_{\pi 12}$ improved with increasing $\omega^2_{\pi 12}$ magnitude. In general all parameters were more accurately estimated with an increase in transition probabilties. Bias of ω^2_{FEV1S2} increased when there was no IIV on π_{12} whereas slight bias in π_{12} disappeared.

Ignoring correlation between the observations in the estimation when correlation was present (ρ = 0.33) resulted in a markedly worse fit as indicated by ΔOFV (Table 1). Estimating a correlation that was not simulated resulted in a range of 100 ΔOFVs that included 0.

Table 1: Average ΔOFV for full and reduced models.

Simulated ρ	$\overline{\Delta OFV}^*$ [range]
π12/π21 = 0.05/0.15	
0	+154 [-1108, 1881]
-0.33	-2981 [-4535, -1486]
π12/π21 = 0.1/0.3	
0	+ 10 [-1493, 1270]
-0.33	- 2830 [-4031, -790]

* ΔOFV: Difference in OFV between the full model including estimation of ρ and the reduced model ignoring the estimation of ρ.

Power to detect a drug effect

The power to detect 3 hypothetical drug effects for the base model with π_{12} and π_{21} equal to 0.05 and 0.15, respectively can be seen in Fig. 4. The BV-MHMM was the most powerful model in all cases.

Figure 4: Power to detect 3 hypothetical drug effects for the BV-MHMM and two univariate models.