Multinomial logistic functions in Markov-chain models for modeling sleep architecture: external validation and covariate analysis

Bizzotto R (1)*, Zamuner S (2), De Nicolao G (3), Gomeni R (2), Hooker AC (4), Karlsson MO (4)

(1) Dept. of Information Engineering, University of Padova, Padova, Italy
(2) Clinical Pharmacology/Modeling&Simulation, GlaxoSmithKline, Verona, Italy
(3) Dept. of Computer Engineering and Systems Science, University of Pavia, Pavia, Italy
(4) Dept. of Pharmaceutical Biosciences, Uppsala University, Sweden

Introduction

- The evaluation of the dynamics of sleep stage distribution through the night is considered a key feature in clinical studies investigating the treatment effects of new molecules for primary insomnia [1].
- A mixed-effect Markov-chain model based on piecewise linear multinomial logistic functions has been recently proposed [2, 3] to characterize the time course of transition probabilities between sleep stages in insomniac patients treated with placebo.

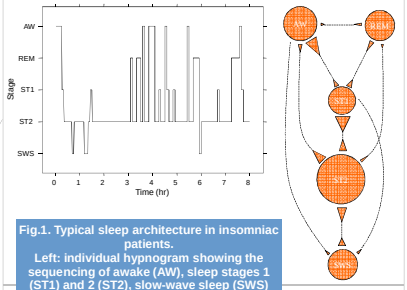

Fig.1. Typical sleep architecture in insomniac patients.
Left: individual hypnogram showing the sequencing of awake (AW), sleep stages 1 (ST1) and 2 (ST2), slow-wave sleep (SWS) and REM sleep (REM).
Right: frequencies of sleep stages (size of circles) and transitions frequencies (size of arrows) in the population.

Objectives

The aims of this work were to

A. further develop the model proposed in [2, 3],
B. perform the external validation of model structure and parameters estimates,
C. explore the covariate effects.

Methods

Data

- Two clinical studies were considered, A and B, with N_A = 116 and N_B = 81 insomniac patients, and similar protocols.
- B was used for external validation only.
- In each study, sequences of sleep stages at each 30-second nighttime interval were obtained from the first night of placebo administration.
- Recorded sleep stages were awake (AW), stage 1 (ST1), stage 2 (ST2), slow-wave sleep (SWS) and REM sleep (REM).

Multinomial logistic functions in a Markov-chain model

- The time course of sleep stages was assumed to obey to a Markov-chain model, and a population approach was implemented with NONMEM VI. In particular, the relationship between time and individual transition probabilities between sleep stages was modeled through piecewise linear multinomial logit functions [3]:

$$g_{ikm\_r}(t) = log\frac{p_{ikm}(t)}{p_{ikr}(t)} \qquad \text{(Eq. 1)}$$

where $p_{ikm}(t)$ is the probability of moving from sleep stage k at time t-1 to sleep stage m at time t for subject i, and similarly for $p_{ikr}(t)$.

- Five sub-models were built, each one modeling the transitions from a specific sleep stage k.

Development of the model, validation and covariates analysis

A Markov-chain model [2] → Multinomial logit functions [3]

- which ratios?
- correlation for inter-individual variability?
- memory for the Markov-chains longer than 30 seconds?
- different description for transitions during and after initial sleeplessness?
- reduced parameterization (for the time dependence)?

- Model building was based on dataset A and guided by model adequacy criteria (log likelihood ratio test and Akaike information criteria) and internal validation based on simulation (and re-estimation): posterior predictive checks (PPCs) as suggested by Gelman et al. [5], visual predictive checks and visual estimation checks as presented in [4].

B
- External validation of the final model was based on dataset B and relied on the evaluation of objective function values (OFVs), distributions of empirical Bayes estimates (EBEs), parameter values and posterior predictive checks (PPCs) as suggested by Gelman et al. [5].

C
- Age, gender and BMI were explored within NONMEM through stepwise covariate modeling [6] on dataset A. Linear and piece-wise linear additive effects were tested on each logit at each different nighttime break-point.

Results

A
- The final model presented the following specifications with respect to [3]: r equal to k in Eq. 1; significant correlations in sub-models AW, ST1 and ST2; time elapsed since the last change in sleep stage as a further predictor of the logits, through piece-wise linear additive functions; parameters in sub-model AW estimated as different values between initial sleeplessness and rest of the night; reduced number of model parameters (four transition probabilities were fixed to zero and knots number in piece-wise linear functions was reduced to one).
- OFV reduction is shown in Table I (column 3). PPC on study A (Fig. 2) indicated a good agreement between simulated and observed efficacy endpoints in most cases.

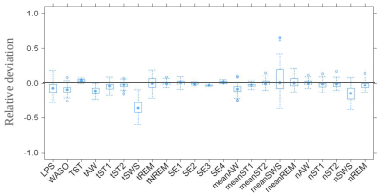

Fig. 2. Results from PPC on study A: relative deviations of median efficacy endpoints in 100 simulated clinical studies from parameter medians in the real study. Represented parameters are: Latency to Persistent Sleep (LPS), Wake After Sleep Onset (WASO), Total Sleep Time (TST), time spent in each stage (tAW, tST1, tST2, tSWS, tREM), time spent in non-REM sleep (tNREM), sleep efficiency in 0-2 hours of bed time (SE1), 2-4 hours of bed time (SE2), 4-6 hours of bed time (SE3), 6-8 hours of bed time (SE4), mean extension of each stage (meanAW, meanST1, meanST2, meanSWS, meanREM), number of transitions to each stage (nAW, nST1, nST2, nSWS, nREM).

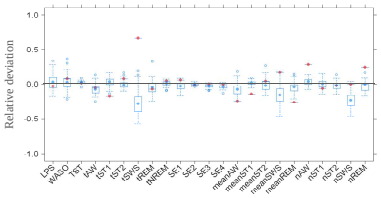

Fig. 3. Results from PPC on study B: median aggregated parameters computed on data B are compared with corresponding median aggregated parameters computed on 100 datasets simulated from parameter values estimated on data B. Comparison is shown in terms of relative deviation. Represented parameters are described in Fig. 1 legend. Red dots are depicted for visualizing the relative deviation of median values computed from study A, from median values computed from study B.

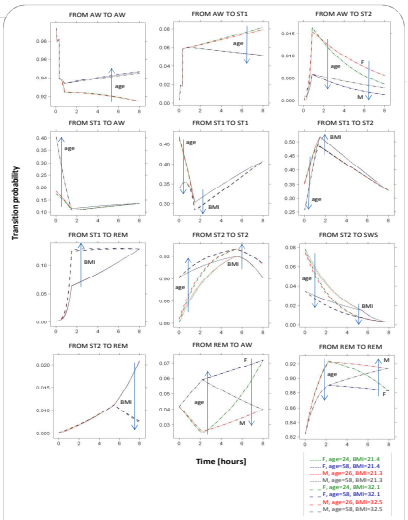

Fig. 4. Covariates effects on the typical individual profiles of some transition probabilities. The computation of probability values is obtained from covariate values chosen as follows: in both the males and females populations of study A, the 5th and 95th percentiles for age and BMI values are computed and used in each of their 4 combinations. Effects are shown only on the transitions for which maximum changes in the probability values using the 4 combinations are greater than 0.01.

B
- Only small and few differences could be found when a comparison between probability profiles estimated from A and B were compared. PPC performance on study B (Fig. 3) looked very similar to the one shown with Fig. 3 on the original data.

C
- Age, gender and BMI were found to linearly affect various model parameters: see Fig. 4 and Table I (column 4). Reduction in inter-individual variability was generally not achieved. The application of PPC to the obtained full model did not show any relevant improvement in model performance.

Table I. OFVs for the 5 sub-models identified on dataset A and B on different scenarios.

sub-model	A, [2]	A, final model *	A, covariate effects inclusion*,#	B, parameter values from A	B, after likelihood maximization§
AW	26983	-5321	-57 (7)	11627	-193
ST1	24264	-178	-16 (2)	19752	-241
ST2	49984	-1251	-28 (3)	33772	-331
SWS	9341	-961	0 (0)	5299	-85
REM	14798	-111	-19 (2)	8906	-95

* delta OFV with respect to column 2
* delta OFV with respect to column 3
# Number of included parameter-covariate relations in parenthesis
§ delta OFV with respect to column 5

Conclusions

- Previously proposed mixed-effect Markov-chain models for describing sleep architecture of insomniac patients treated with placebo [2, 3] were improved in terms of predictive performance and model parsimony.
- The final model was successfully validated with data from a new study.
- Age, gender and BMI were detected as influential covariates: their clinical relevance deserves further exploration in a wider population of insomniac subjects.

References

- [1] Gimenez S et al. Psychopharmacol 2007; 190:507–16.
- [2] Karlsson MO et al. Clin Pharmacol Ther 2000; 68(2):175-88.
- [3] Bizzotto R et al. J Pharmacokinet Pharmacodyn 2010; 37:137-55.
- [4] Mezzalana E et al. PAGE 19 2010; Abstr 1893.
- [5] Gelman A et al. Bayesian data analysis. Chapman & Hall 1995, London, UK.
- [6] Jonsson EN et al. Pharm Res 1998; 15(9):1463-8

*E-mail: roberto.bizzotto@gmail.com