Multinomial logistic functions in Markov-chain models for modelling sleep architecture after placebo administration

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Introduction

The evaluation of the dynamics of sleep stages distributing along the night is considered a key feature in clinical studies investigating the treatment effects of new molecules for primary insomnia [1]. In particular, the transitions from different stages are informative of different sleep patterns in the insomnia patient as well as of potential treatment benefits. Sleep stages can be assessed for each subject - through polysomnographic recordings - as awake state (AW), sleep stages 1 (STG1) and 2 (STG2), slow-wave sleep (SWS) and REM sleep (REM) (see Fig. 1 for typical sequence of sleep stages and frequency during the night).

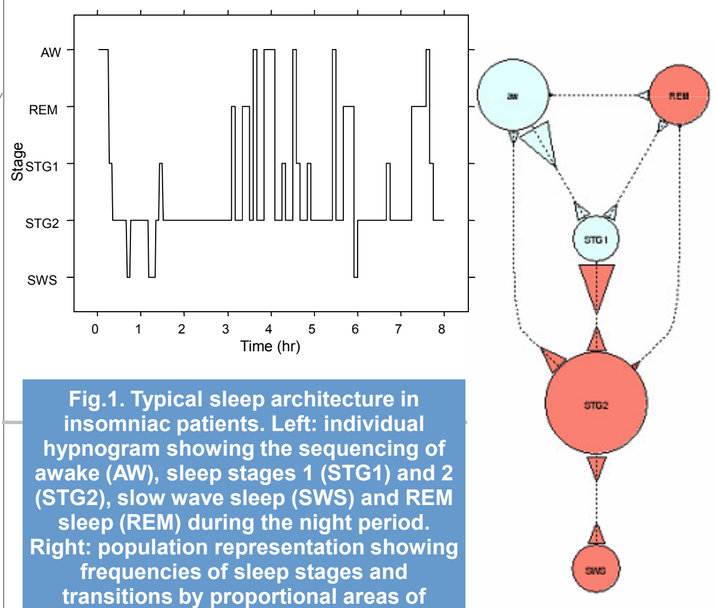

Fig.1. Typical sleep architecture in insomniac patients. Left: individual hypnogram showing the sequencing of awake (AW), sleep stages 1 (STG1) and 2 (STG2), slow wave sleep (SWS) and REM sleep (REM) during the night period. Right: population representation showing frequencies of sleep stages and transitions by proportional areas of circles and arrows, respectively.

Objectives

The aim of this work was to generalize the previously proposed [2] mixed-effect Markov-chain model based on piecewise linear binary logistic functions through the implementation of multinomial logistic functions, in order to characterize the time course of transition probabilities between sleep stages in insomniac patients.

Methods

Data

Polysomnography data were obtained from the first night of a placebo-controlled treatment in insomniac patients.

Multinomial logistic functions in a Markov Model

The time course of sleep stages (awake, stage 1, stage 2, slow-wave sleep and REM sleep) 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 logistic functions. For example, when modeling transitions from SWS, four multinomial logit functions can be defined as:

$$g_{1T} = \log \frac{\Pr(AW_T \mid SWS_{T-1})}{\Pr(ST2_T \mid SWS_{T-1})},$$

$$g_{2T} = \log \frac{\Pr(ST1_T \mid SWS_{T-1})}{\Pr(ST2_T \mid SWS_{T-1})},$$

$$g_{3T} = \log \frac{\Pr(SWS_T \mid SWS_{T-1})}{\Pr(ST2_T \mid SWS_{T-1})},$$

$$g_{4T} = \log \frac{\Pr(REM_T \mid SWS_{T-1})}{\Pr(ST2_T \mid SWS_{T-1})}.$$

Using these equations and recalling that the sum of the three probabilities conditional on SWS_{T-1} must be equal to one, the transition probabilities can be derived from the logits:

$$\Pr(AW_T \mid SWS_{T-1}) = \frac{\exp(g_{1T})}{1+\exp(g_{1T})+\exp(g_{2T})+\exp(g_{3T})+\exp(g_{4T})},$$

$$\Pr(ST1_T \mid SWS_{T-1}) = \frac{\exp(g_{2T})}{1+\exp(g_{1T})+\exp(g_{2T})+\exp(g_{3T})+\exp(g_{4T})},$$

$$\Pr(ST2_T \mid SWS_{T-1}) = \frac{1}{1+\exp(g_{1T})+\exp(g_{2T})+\exp(g_{3T})+\exp(g_{4T})},$$

$$\Pr(SWS_T \mid SWS_{T-1}) = \frac{\exp(g_{3T})}{1+\exp(g_{1T})+\exp(g_{2T})+\exp(g_{3T})+\exp(g_{4T})},$$

$$\Pr(REM_T \mid SWS_{T-1}) = \frac{\exp(g_{4T})}{1+\exp(g_{1T})+\exp(g_{2T})+\exp(g_{3T})+\exp(g_{4T})}.$$

The choice of the multinomial model was motivated by the following reasons: (1) to assure that the sum of all probabilities of transitions starting from a certain stage is equal to one; (2) to reduce the number of sub-models to be identified: from 20 sub-models using the binary-logit approach to 5 sub-models in the new approach (one for each sleep stage); (3) to estimate probabilities of all transitions at any time avoiding the need for a preliminary analysis aimed to identify zero-probability transitions.

Model Performance

Performance was evaluated through visual inspection of model fitting on post-hocs and through posterior predictive check as suggested by Gelman et al. [3].

Results

Probabilities of transition between all stages where estimated together with their inter-individual variability, and uncertainty on sleep dynamics description was evaluated applying bootstrap technique (Fig.2). The identification of the five sub-models produced a good adherence of mean post-hocs to the observed transition frequencies (Fig. 3). Parameters were generally well estimated in terms of CV, shrinkage and distribution of empirical Bayes estimates around the typical values.

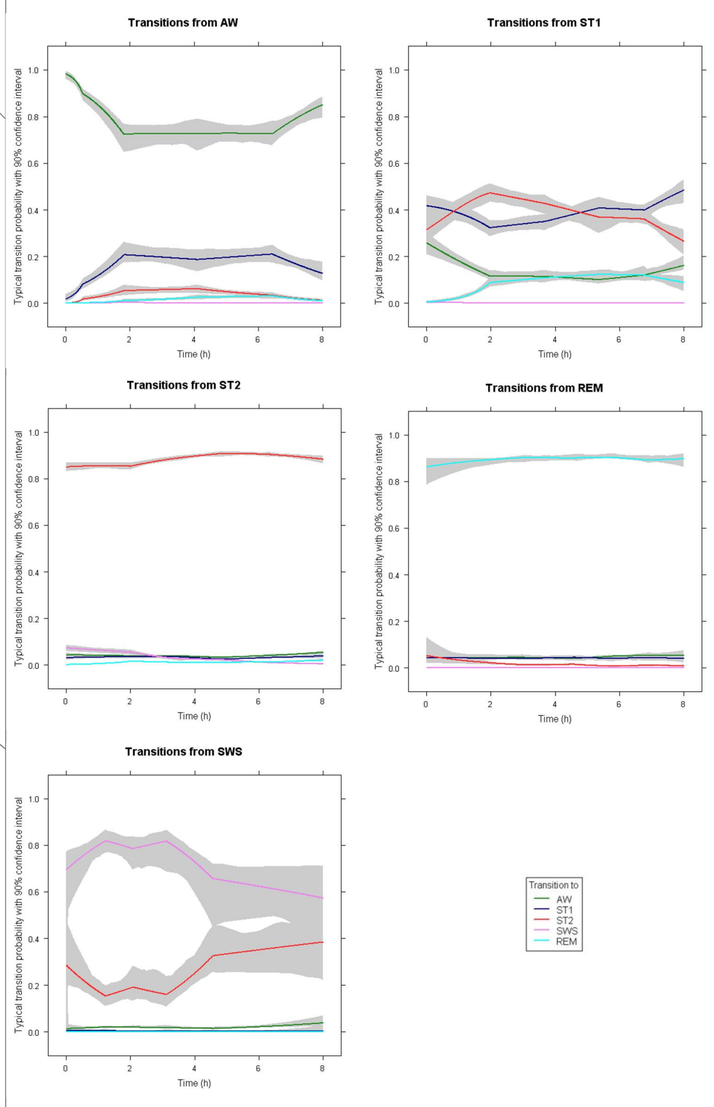

Fig.2. Estimated time course of typical transition probabilities with 90% confidence intervals from bootstrap; each panel shows the transition probabilities from a specific sleep stage.

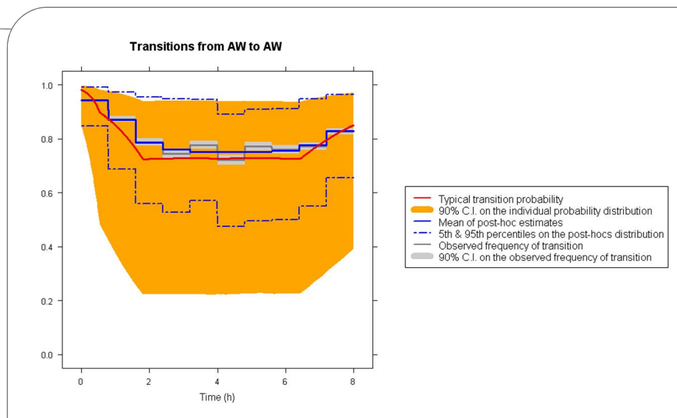

Fig.3. Observed time profile of a transition frequency chosen as example, with 90% confidence intervals; distribution of post-hoc estimates (as mean and 5th-95th percentile); estimated profile of the typical transition probability and 5th-95th percentile of the distribution of individual profiles.

The posterior predictive check showed good adherence of most of the simulated distributions of sleep macro parameters to the observed parameter values (Fig. 4). A slight overestimation of the transition probabilities from the slow-wave sleep stage to other stages was found. This outcome may be explained by the small number of occurrences of these transitions, although further work is needed to investigate the reason for this finding.

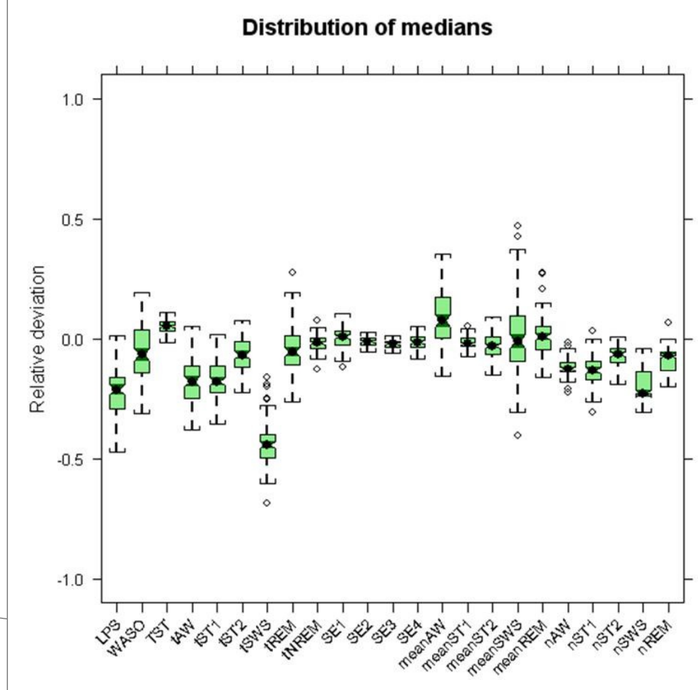

Fig.4. Results from posterior predictive check: relative deviations of median efficacy endpoints in 100 simulated clinical studies from parameter medians in the real study. Represented parameters are: Latency to Persistent Sleep (LPS), Wake After Sleep Onset (WASO), Total Sleep Time (TST), time spent 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).

Conclusions

- This work confirms the adequacy of mixed-effect Markov-chain models for describing sleep architecture of insomniac patients treated with placebo.
- Moreover, the use of multinomial logit functions in place of binary ones yields physiologically constrained parameters, reduces the influence of exploratory data analysis, and requires the identification of fewer sub-models.

References

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