Multinomial logistic functions in Markov-chain models for modeling sleep architecture: internal validation based on VPCs and VECs

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Introduction

- Simulation based diagnostics are increasingly used to illustrate model properties [1], especially in the context of categorical data.
- 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 (nominal data) in insomniac patients treated with placebo.
- 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.

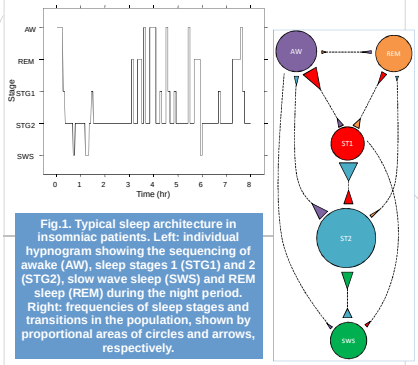

Fig.1. Typical sleep architecture in insomniac patients. Left: individual hypnogram showing the sequencing of awake (AW), sleep stages 1 (STG1) and 2 (STG2), slow wave sleep (SWS) and REM sleep (REM) during the night period. Right: frequencies of sleep stages and transitions in the population, shown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

Objectives

The aim of the present work was to perform the internal validation of this model using simulation based diagnostic methods.

Methods

Data

Data were obtained from the first-night of polysomnographic (PSG) recordings from 116 subjects diagnosed with primary insomnia and belonging to the placebo arm of a PSG-parallel study. Sleep stages were recorded at each 30-second nighttime interval as awake (AW), stage 1 (ST1), stage 2 (ST2), slow-wave sleep (SWS) and REM sleep (REM).

Multinomial logistic functions in a Markov Model

Each individual time course of sleep stages was assumed to obey to a Markov-chain model, implemented with NONMEM VI and estimated with the LAPLACE option. In particular, the relationship between time and individual transition probabilities between sleep stages was modeled through piecewise linear multinomial logit functions [2]:

$$g_{ikm}(t) = log\frac{p_{ikm}(t)}{p_{ikk}(t)}$$

where $p_{ikm}(t)$ is the individual probability of moving from sleep stage k at time t-1 to sleep stage m at time t, and similarly for $p_{ikk}(t)$.
The transition probabilities can be therefore derived from the logits as:

$$p_{ikm}(t) = \frac{exp(g_{ikm}(t))}{\sum_{m\in S} exp(g_{ikm}(t))}$$

where S={AW, ST1, ST2, SWS, REM} is the state-space.

Simulation based diagnostic methods

Model performance was evaluated through the implementation of diagnostic methods based on stochastic simulations (and re-estimation + computation): '*Visual Predictive Check*' (VPC) and '*Visual Estimation Check*' (VEC).

- VPCs were performed to evaluate potential model misspecification and model robustness (uncertainty of model parameters estimates). Each VPC was based on 100 datasets simulated from point estimates of model parameters. In particular, transition frequencies and fractions of observations for each stage were calculated from observed data considering ten intervals of the night with equal width, and compared to the 95% confidence interval derived from simulated datasets on the same intervals [4].
- VECs allow the evaluation of both model performance and estimation method in an easily understandable visual form. Typical transition probabilities and the 5th and 95th percentiles of individual transition probabilities distribution along the night estimated from the original data were compared with probabilities derived from the estimates of simulated data. This is shown schematically below: the 'computation' block is innovative compared with methods presented in literature [5].

SIMULATION of *n*=100 datasets from the point estimates of model parameters derived from raw data → RE-ESTIMATION of the model parameters for each simulated dataset → COMPUTATION of the transition probabilities profiles from the estimated parameters of each dataset

Results

The VPCs showed in general a good agreement between the statistics derived from raw and simulated data. Most of the transitions among sleep stages were well characterized in terms of parameters accuracy and precision (Fig. 2).

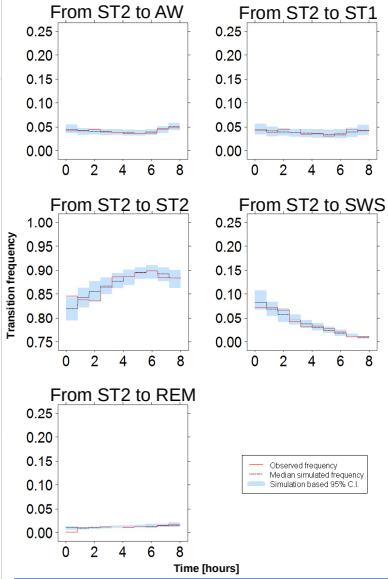

Fig.2. Some results from VPCs: time course of transition frequencies from ST2 with their corresponding 95% confidence intervals derived from simulations and simulated median transition frequency.

The VECs showed good adherence between the estimated transition probability profiles (typical and 5th and 95th percentiles on inter-individual variability, IIV) and the corresponding confidence intervals derived form simulations and re-estimations (Fig.3).

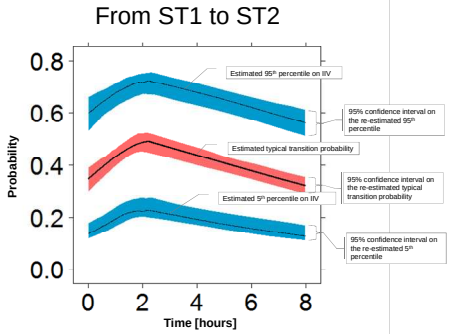

Fig.3. Results from VECs on the transition probability from ST1 to ST2.

A slightly higher uncertainty was observed for the transitions from slow-wave sleep and from REM sleep (Fig. 4). This result is likely due to the limited occurrences of these transitions.

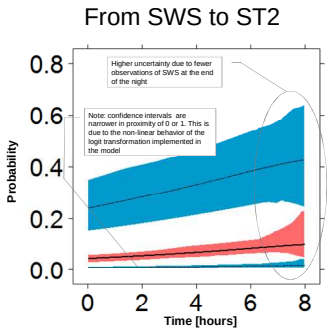

Fig.4. Results from VECs on the transition probability from SWS to ST2.

Conclusions

- Through the implementation of VPCs on the transition frequencies and the frequencies of stage occurrence, the model was demonstrated to be appropriate for describing the physiological evolution of the considered statistics along the night.
- An innovative visual diagnostic method (VEC) was implemented in this framework. According to VECs results, the Markov-chain model was adequate to describe the available categorical data and the estimation method used in this analysis resulted unbiased.

References

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