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Summary

The EEG during sleep shows a recurrent cycling pattern of EEG activity representing alternating phases of NREM sleep and REM sleep. These dynamical changes between sleep behavioral states are only poorly described by visual sleep scoring and conventional spectral analysis of the sleep EEG. This review presents a novel model based approach for sleep EEG analysis (state space model) that allows for a more dynamical description of sleep EEG. Basic principles of mathematical modeling and EEG signal analysis are also reviewed and illustrated.

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Key words: Sleep, EEG, mathematical modeling, state space analysis

L'EEG du sommeil en « state space model »

L'EEG du sommeil présente des motifs distincts récurrents, correspondant aux différentes phases cycliques de l'activité cérébrale au cours du sommeil. Ces changements dynamiques entre les phases de sommeil sont cependant faiblement décrits par l'analyse conventionnelle de l'EEG, qu'elle soit visuelle ou spectrale. Cette revue présente un nouveau modèle mathématique d'analyse de l'EEG du sommeil (« state space model »), qui permet une meilleure description des aspects dynamiques de l'EEG. Les principes de la modélisation mathématique et de l'analyse du signal EEG sont également examinés et illustrés.

Mots clés : EEG du sommeil, modélisation mathématique, state space analysis

Das Schlaf-EEG im « state space model »

Das EEG im Schlaf zeigt wiederkehrende Muster unterschiedlicher EEG-Aktivität, welche den zyklischen Wechsel zwischen verschiedenen Schlafzuständen repräsentieren (NREM-REM-Schlafzyklus). Die konventionelle Schlaf-EEG-Analyse durch visuelles Scoring oder Spektralanalyse kann diesen dynamischen Wechsel zwischen verschiedenen Schlafstadien nur unzureichend beschreiben. Dieser Übersichtsartikel präsentiert eine neue mathematische Methode der Model-basierten EEG-Analyse, welche die dynamischen Aspekte des Schlaf-EEGs besser zur Darstellung bringt und quantifiziert. Die Grundlagen der mathematischen Modellierung und der EEG-Signalanalyse werden im Artikel ebenfalls behandelt.

Schlüsselwörter: Schlaf, EEG, mathematische Modellierung, state space analysis

Mathematical modeling

The scientific approach to a quantifiable problem can be divided in data acquisition (observations) and interpretation of observations based on assumed mechanisms or underlying rules (concepts). Phenomena and observations take place in the external or "real world", where events are observed and then translated to a "conceptual space". In the conceptual space, analysis and interpretation of events can be performed in a model based approach [1]. A model can be thought of as a simplified reflection of reality to interpret and conceptualize observations in the real world. A model in this broad sense can have many forms: e.g. a regression curve, a block diagram or a sketch on the back of an envelope. Modeled data and model-based predictions are then compared to past (real world) observations and can be tested on novel experimental observations in a train-test approach [2]. Mathematical and computational modeling has advantages in analyses with large amount of data and complex interactions within the system that do not allow for direct interpretation of experimental observations.

Usually, the first step after the implementation of a computational model is to reproduce known observations and previously observed effects. An accurate description of known phenomena is a basic condition for a comprehensive and well-designed model. However, the mere replication of known observations reveals little new knowledge and the question arises: what can be learned from mathematical modeling? As discussed in more detail in the next paragraph, a model based approach can have a two-fold impact by (i) predicting future outcome and (ii) improving the understanding of interactions and causal relationships within a complex system.

For illustration, let's consider the example of weather forecasting. Observing blue sky (in the "real world") today, there is a fair chance that tomorrow the weather will be good, too. Technically speaking, this conclusion derives from a simple model that predicts the weather tomorrow from today's weather based on previous experience. In other words, the brain performs a Markovian analysis on the time series of rainy and sunny days [3]. This model therefore provides a (very simple) prediction of the future weather and can be compared to observations in the real world ("is it really sunny tomorrow?") and it can be verified that this model describes the weather in a short term temporal evolution accurately [4]. However, using this model we still haven't learned much about the underlying mechanisms of weather changes. If we consider a more complex climate model (e.g. modeling long term climate changes from climate data), computational approaches are needed to handle the large amount of multidimensional and interconnected data. Now, if we manage to create an accurate mathematical model of such a system, the possibility arises to tackle a mechanistic question: A model-based approach on slow cyclic climate changes ("el nino years") predicted for example, that solar activity has a predominant effect on the modeled temporal evolution of the climate [5]. Thus, this model delivered a novel hypothesis that could be tested (and verified) by direct observations and correlative analyses in later experiments. Here, the computational approach has revealed an unknown mechanism that was concealed by the overwhelming amount of data.

In summary, the ideal mathematical model describes known observations accurately, predicts future outcome and delivers novel insights in the underlying mechanisms of the observed system. But why do we need a model based approach to sleep EEG?

Sleep architecture and spectral analysis of sleep EEG

Since the introduction of the electroencephalogram (EEG) into clinical practice and neuroscience, different sleep behavioral states have been identified and characterized. From a broad perspective, humans (and most other animals) show two distinct sleep behavioral states: REM sleep and non-REM sleep [5, 6]. The EEG in non-REM sleep is characterized by slowing background activity, sleep spindles, K-complexes and in its most pronounced state by synchronized high amplitude and low frequency oscillatory activity (also referred to as slow wave sleep). REM sleep, on the other hand, shows higher frequency and lower amplitude EEG activity similar as in the waking state. The term "paradoxical sleep" has therefore been introduced by Jouvet and coworkers after the discovery of REM sleep in rodents [8]. Despite the continuous and rather unspectacular absence of consciousness during physiological sleep, the nocturnal EEG reveals a changing sequence of these patterns of cortical activity. Furthermore, physiological sleep shows a cycling pattern with alternating phases of NREM sleep and REM sleep (NREM-REM cycles) that repeat periodically approximately every 90 minutes [9]. The term sleep architecture is used to describe the alternating sequence, global structure and temporal variability of sleep behavioral states and can be summarized graphically in a hypnogram (**Figure 1A**).

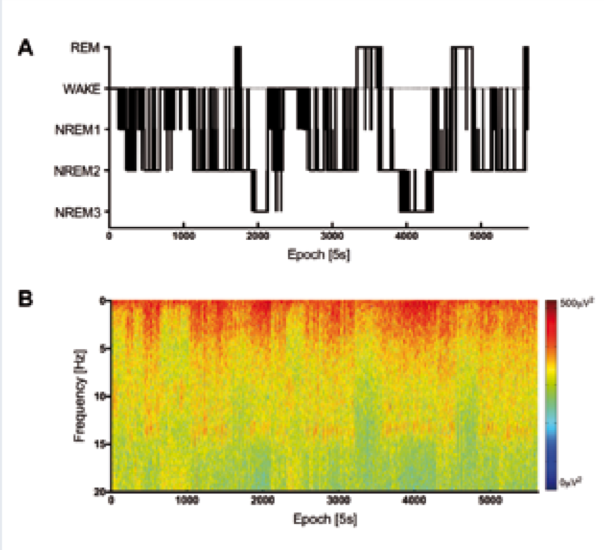

Figure 1. Conventional sleep analysis.
(A) The hypnogram represents sleep stages as a function of time. 5 s epochs are represented for each behavioral state as visually scored. NREM: non-REM sleep; REM: REM-sleep; WAKE: waking state.
(B) The time frequency spectrogram represents power spectral density of consecutive 5 s epochs as calculated by a Fourier transformation algorithm. Epochs are multiplied by a Hann window to address edge discontinuities.

Beyond the behavioral description of sleep, spectral analysis of sleep EEG provides a quantifiable approach to EEG signals. Fourier transformation is the most commonly used method for spectral decomposition of the EEG into a linear superposition of harmonic oscillations. The introduction of spectral EEG analysis dates back to the 1930ies, when Dietsch and Berger introduced quantitative frequency analysis to the human EEG [10]. Digitalization of brain signals and advances in computational methods (e.g. the introduction of fast Fourier transformation) have led to an increased use of quantitative spectral analysis to EEG in general and the sleep EEG in particular [11]. Whereas in recent years, non-linear methods of data analysis are gaining influence in EEG data analysis in many fields, spectral analysis still has a predominant role in the analysis of sleep EEG for several reasons. Most importantly, sleep EEG – although clearly non-deterministic – can be approximated as a stationary signal and therefore analyzed by linear methods (such as Fourier transformation) on a short time scale. In other words, by applying Fourier transformation analysis on sleep EEG, we assume that the intrinsic properties of the EEG signal does not change over the time span under consideration. For example, if a 30 s epoch of slow wave sleep is divided into smaller epochs of 5 seconds length, the signal characteristics in these smaller epochs do not change significantly (i.e. this signal is "stationary"). Furthermore, spectral analysis of sleep EEG has revealed fundamental differences between sleep stages and has provided even defining properties of sleep behavioral states. For example, increased slow oscillatory EEG activity is the fundamental property of NREM sleep (**Figure 1B**). A comprehensive review of spectral methods in the analysis of sleep EEG can be found in [12].

These qualitative and quantitative approaches of sleep EEG analysis have been used extensively and describe many aspects of sleep accurately. However, these "conventional" approaches rely on manual scoring of 30 s epochs and therefore dynamical aspects of changes between sleep behavioral states are not, or only poorly described [13]. Therefore, our group recently established a model based approach [13] a model-based approach to sleep EEG emphasizing the dynamical changes between sleep behavioral states.

Introduction of the state space model

Sleep analysis by manual scoring of sleep behavioral states is the gold-standard for clinical sleep assessment. However, conventional scoring in 30 s epochs limits analysis of dynamic properties of sleep EEG. In particular, transitions between sleep behavioral states are poorly described. Conventional scoring of sleep behavioral states in 30 s epochs presents transitions between behavioral states as if they were instantaneous, though the visual appearance and spectral analysis of the EEG suggests the transitions to be gradual with intermediate patterns of EEG activity. For example, in a transition from wake into deep sleep, slow decrease of alpha activity and increase in delta power are observed at the same time indicating a "transitional state" between otherwise well-defined stable sleep stages.

To allow for a more dynamic analysis of sleep EEG a novel method of EEG analysis has been introduced in rodents [14 - 16] and was adapted for analysis of healthy and pathological sleep in humans [13, 17]. In this approach, behavioral changes are described in a 2-dimensional state space that is derived from spectral characteristics of the EEG. Importantly, by automated spectral analysis of subsequent EEG-epochs, this approach allows for a quantitative and un-biased analysis of the temporal dynamics of sleep.

A detailed explanation of the method and an accurate mathematical description can be read elsewhere [13]. Briefly, in state space EEG analysis, the spectral information of each sleep EEG epoch is transformed into a 2-dimensional space by calculating two different frequency ratios of previously determined frequency bands. First, for each 5 second epoch, the power spectral density function is estimated by calculating its fast Fourier transformation [3]. For a discrete signal of length T (defined in the period [-T/2,+T/2], it can be shown that the squared amplitude of the Fourier transform can be taken as an approximation of the power spectral density (PSD) of the original signal. The state space is then constructed by calculating two different frequency ratios from previously determined frequency bands [13]. Thus, each EEG epoch is finally represented by two real valued numbers (ratio1 and ratio2) or as a point in the corresponding 2-dimensional state space. A whole night polysomnography is therefore described as a scatterplot with clusters representing the different sleep behavioral states (**Figure 2A**). However, in contrast to conventional spectral analysis or conventional sleep scoring, transitions between and within sleep states result in trajectories in the state space.

We have adapted this model to human sleep EEG and optimized the parameters (i.e. the frequency bands) in a probabilistic Bayesian approach on sleep EEG of healthy controls. The optimized model has proven to adequately replicate manual sleep scoring by sleep experts and automated sleep state scoring on model naïve data had a mean positive predictive value of 80% to match manual scoring (which is similar to inter-expert variability) [13].

Thus, by reproducing current state-of-the-art concepts (sleep state scoring on a fixed time frame using sleep scoring rules), the state space model fulfills the first condition for a model based approach.

Novel insights using the model based approach

However, what can we learn from the model based approach to sleep EEG beyond the replication of (predefined) human scoring rules? The state space approach to the sleep EEG reveals the possibility to explore sleep in at least two new dimensions: the analysis of topographic and dynamical sleep characteristics [13].

The topography of sleep in the state space refers primarily to cluster arrangement. During consolidated phases of sleep (e.g. stable slow wave sleep), the state space model generates clusters (**Figure 2A**). This finding implicates that in consolidated sleep, the EEG has little spectral variance, because location in state space translates to spectral similarity. In other words, "clustered sleep" refers to stable and consolidated sleep EEG [13]. However, individual cluster distribution differs between individuals and can be altered in pathological sleep. For example, in a mouse model of narcolepsy, clusters of WAKE and NREM sleep were found to be less separated as compared to control animals [15]. In other

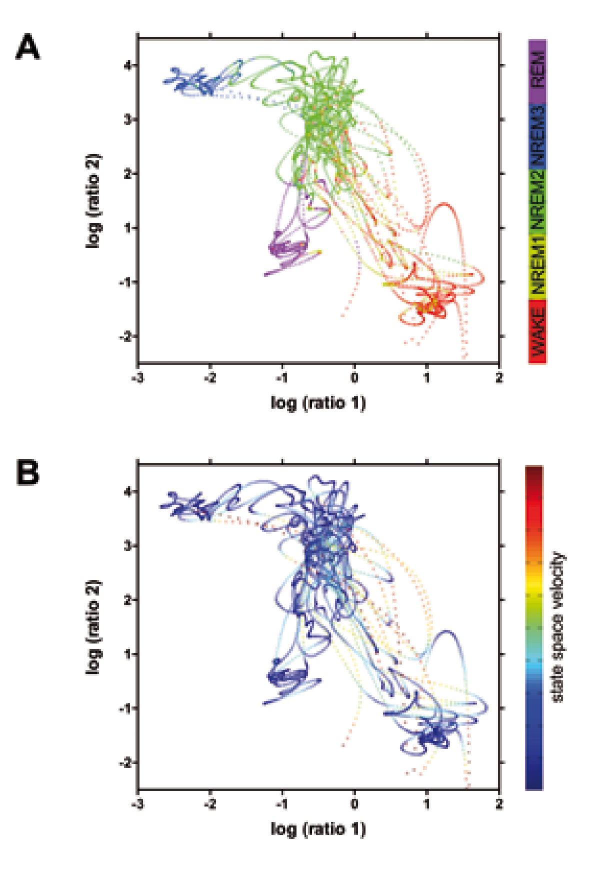

Figure 2. Sleep state clusters and state space velocity.
(A) State space analysis of a whole night polysomnography is shown for one control subject. Each 5 s EEG epoch (raw data) is represented by 2 different frequency ratios plotted on log/log axes. Ratio1=(8.6 to 19.3 Hz)/(1.0 to 10.9 Hz), Ratio2=(11.5 to 20.3 Hz)/(17.9 to 31.5 Hz). Color coding of the clusters is based on expert scoring for WAKE (red), NREM stage 1 (yellow), stage 2 (green), stage 3 (blue), and REM sleep (magenta).
(B) The same EEG trace is analyzed and color coded by state space velocity (right sided color bar, [a.u.]). Stable clusters show low velocity values with points closely spaced (darker colors), whereas transitional states show higher velocities with points widely spaced (lighter colors). Note that low velocity states form clusters in state space, whereas high velocity states correspond to transitional states.

words, the mathematical model revealed that in narcoleptic mice the difference between behavioral states is less distinct. Therefore, this finding can be interpreted as a quantification of state-boundary dysfunction in narcolepsy [9, 18].

Regarding dynamical aspects, the state space model describes transitional states as trajectories between consolidated clusters. Manual scoring of these states is often difficult and ambiguous, because transitional states typically lack a distinct spectral pattern that is required by the scoring rules. Here, the state space model provides a smooth and continuous description of transitional states (**Figure 2**). Transitional states are also characterized and quantified by state space velocity. Velocity in state space (defined as the Euclidean distance between two subsequent states divided by the time interval between these states) is a measure of sleep state stability: High velocity states correspond either to rapid transitions between states or fluctuations within a state, whereas low velocity states form consolidated clusters [13, 17]. Analyzing sleep trajectories, we found that velocities in state space in 5 s intervals increased abruptly during transitions between behavioral states [13].

The state space model in pathological sleep

Using this concept we have applied the state space model to sleep EEG of Parkinson's patients and calculated state space velocity in PD patients and controls as a measure of altered sleep dynamics. We found that Par-

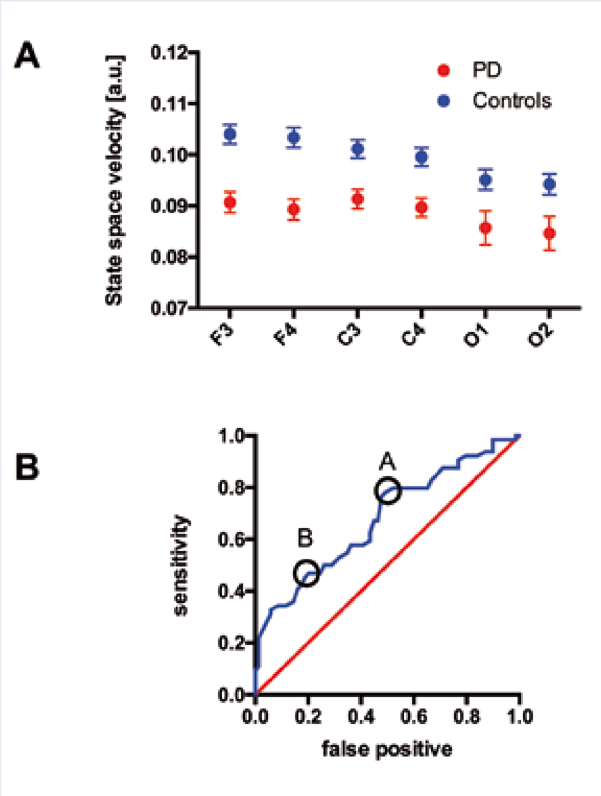

Figure 3. Reduced state space velocity (Bradysomia) in Parkinson's patients and healthy controls.
(A) At all electrodes, PD patients had significantly lower average velocities as compared to healthy controls (adapted from [17]).
(B) Receiver operating characteristic (ROC) analysis for state space velocity as a potential biomarker for PD as compared to healthy controls. Each point on the curve represents the sensitivity (true-positive rate) and false-positive rate (1 - specificity) associated with a particular value for state space velocity (range: 0.05 - 0.14, Point A: high sensitivity/low specificity. Point B: low sensitivity/high specificity.

kinson's patients have a significantly lower state space velocity as compared to controls, i.e. changes in sleep EEG are less dynamic as compared to healthy sleepers [17]. In the terminology of the state space model, Parkinson's patients are therefore "slow sleepers" and in analogy to bradykinesia or bradyphrenia in Parkinson's patients, we introduced the term bradysomnia for this novel observation (**Figure 3A**). Thus, the model-based finding created the hypothesis that sleep in Parkinson's disease is less dynamic and sleep architecture might be less modulated. Indeed, we found, that the observed reduction in state space velocity (corresponding to impaired sleep wake dynamics) correlates significantly with arousability (as measured conventionally by the arousal index) [17]. Furthermore, we found that state space velocity might serve as a diagnostic tool for Parkinson's disease (**Figure 3B**) and a receiver operating characteristic (ROC) analysis showed the feasibility of using this measure as a diagnostic tool [17]. However, this retrospective study obviously does not validate this measure in terms of predictive diagnostic values in a clinical setting. Nevertheless, this example illustrates the link between a model derived finding in the "conceptual world" (bradysomnia) with novel observations in the "real world" (reduced arousability in Parkinson's disease) and its potential use in clinical practice.

Conclusion

The sleep EEG is a complex and highly dynamic electrophysiological signal and is classically analyzed by visual scoring of 30 s epochs. Spectral analysis of sleep EEG provides a quantitative approach to sleep EEG and many aspects of sleep are well represented in this approach. However, dynamical aspects of sleep and spectral variability are only poorly described. Describing sleep EEG in a model based approach allows for an unbiased quantitative description of sleep with emphasis on the dynamical (transitional) sleep phases. The model based approach has proven to be applicable to healthy and pathological sleep in rodents and humans. Controlled studies using this model have revealed novel insights on the regulation of sleep wake dynamics. Furthermore, a model driven analysis may provide novel quantitative measures that are changed in pathological sleep and might even be used as a diagnostic tool. Future studies might include other groups with suspected state boundary dyscontrol (e.g. patients with narcolepsy). Finally, the state space approach is in principle not limited to sleep EEG. For example, dynamic changes of EEG in coma patients are difficult to estimate visually and might be quantifiable using the state space approach.

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