# The spectral slope of the EEG as an indicator of sleep depth and architecture

## PhD thesis

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# 1 Introduction

In the study of the electric activity of the brain most commonly oscillations are in the focus, yet neural activity comprises an ever-present stochastic, wide-band component, observable on multiple scales, from fluctuations of membrane potentials to the scalp electroencephalography (EEG). Based on observations that the aperiodic, fractal background component reflects meaningful information about states of arousal and consciousness, we adopted a model of the EEG frequency spectrum that captures the aperiodic component using a power-law linking the frequency and power spectral density, then assessed how parameters of this model reflected different aspects of sleep.

# 2 Objectives

First, we aimed to assess the effects of sleep stage, sex, age and brain region on the spectral parameters of the EEG during sleep in a healthy population, in search of mathematically well-defined markers of objective sleep depth.

Second, to provide an algorithm for sleep cycle detection utilizing the overnight dynamics of the spectral slope, and compare the newly defined cycles to classical, manually annotated ones. Besides testing the cycle detection algorithm on a healthy sample, sleep data from major depression disorder patients was included in our analysis, in an attempt to test our method's sensitivity to alterations in sleep structure present due to the disorder and different types of antidepressant medications.

Overall, the objectives of our work had been to explore the behavior of fractal parameters during sleep in more detail, and at the same time to lay the foundations of a more objective, quantitative methodology of sleep depth and structure measurement, alternative to time-consuming and potentially subjective sleep staging and cycle annotation.

# 3 Methods

## 3.1 Study 1 - Scale-free and oscillatory spectral measures of sleep stages in humans

### 3.1.1 Materials and Equipment

In the first study EEG recordings from the Budapest-Münich polysomnographic database were used that included 251 healthy subjects (122 females) from a wide age range (4-69 years). Age groups were defined as: children (4–10 years, N = 31), teenagers (10–20 years, N = 36), young adults (20–40 years, N = 150), and middle-aged adults (40–69 years, N = 34). Ten EEG channels were analysed with placements according to the 10-20 standard.

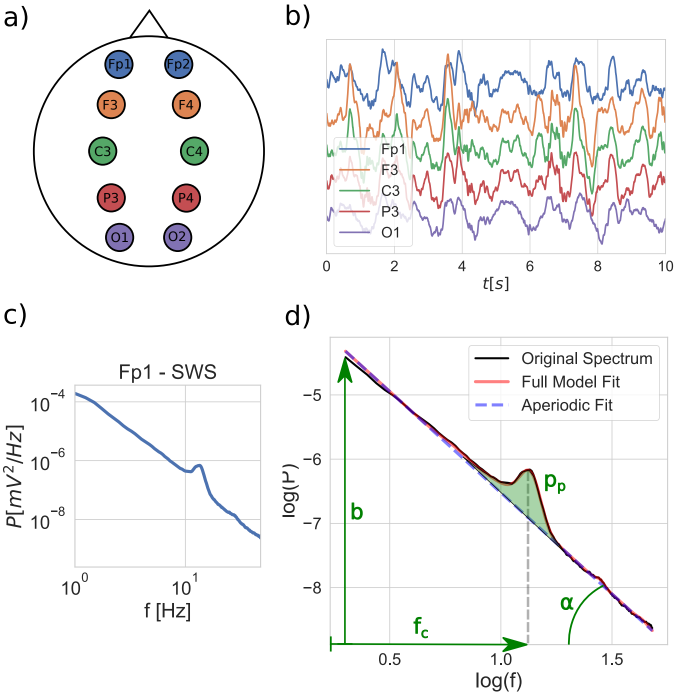

Figure 1: Schematic outline of the fitting process: **a)** EEG is recorded with electrodes placed according to the 10–20 system, out of which 10 are used, covering 5 brain regions on both left and right hemispheres. **b)** Time domain signals are segmented into 20 s windows and grouped by sleep stages for each EEG channel. **c)** Average power-spectral density is calculated for each sleep stage per channel. **d)** The FOOOF model is fitted to the average power spectra, and the model parameters are extracted: spectral slope [$x = tan(\alpha)$], intercept (b), peak central frequency ($f_c$), and peak power ($p_p$).

### 3.1.2 Power spectrum calculation

The power-spectral densities (PSDs) were calculated for each sleep stage, subject and electrode. The signals were segmented into windows of 4$s$ length with 2$s$ overlap, windows that contained any artifacts were excluded, than a Hanning-window was applied, and the squared absolute values of the FFT evaluated. Average PSDs for each subject, electrode and sleep stage were created using Welch's method.

### 3.1.3 Model fitting

The spectral slope and intercept along with spectral peaks parameters were extracted from each PSD using the "Fitting of Oscillations and One Over F" (FOOOF) method.

The fitting was applied to the 2-48 Hz frequency range, resulting good fits in general. Some parameters of the method were altered in order to avoid over- and underfitting.

### 3.1.4 Statistical analysis

The parameters included in the statistical analyses were: the spectral slope, center frequency and power of the dominant peak. Considering each spectral parameter as the dependent variable, general linear model analysis (repeated measures ANOVA with sigma restricted parametrization) was carried out while considering factors of sex and age group, and within-subject effects of sleep stage: WAKE, NREM1, NREM2, SWS, REM, brain region and laterality.

## 3.2 Study 2 - Fractal cycles of sleep, a new aperiodic activity-based definition of sleep cycles

In the second study a novel sleep cycle detection method had been introduced, based on the overnight dynamics of the spectral slope of the fractal EEG component. The newly defined 'fractal cycles' were compared to classical, manually annotated sleep cycles, assessing correlations of cycle durations between the two methods, as well as the detection of skipped REM stages in a population of healthy subjects and a group of patients with major depressive disorder (MDD).

### 3.2.1 Materials

A total of 337 polysomnographic recordings were used to compare the two methods, combined from six datasets, that included 205 healthy adults from a wide age range of 18-75 years (mean: $36.7 \pm 15.0$ years), 118 females (Datasets 1-5) and 21 healthy children and adolescents between the ages of 8 and 17 years (mean: $12.4 \pm 3.1$ years), (Dataset 6). Datasets 1-3 also included 111 patients with MDD. EEG electrodes F3 and F4 were used as these were most common in all datasets.

### 3.2.2 Fractal activity-based cycles of sleep

The proposed method aims to give an objective, automatically computable definition of sleep cycles based on the fractal (or aperiodic) activity of the brain, more precisely the local extrema in the overnight dynamics of the spectral slope of the electroencephalogram.

Power spectra were calculated for each epoch and the fractal component separated from the oscillatory spectral component using the Irregular-Resampling Auto-Spectral Analysis (IRASA) method. The spectral slopes were then calculated in the log-log domain in the $0.3 - 30$ Hz frequency range.

The time-series of slope values were normalized by converting them into a series of z-scores per recording, then smoothed. Next, a peak detection algorithm was employed to find the local minima and maxima of the smoothed series, with 20 minute minimal distance between peaks and peak prominence of $|z| > 0.9$. Having detected the local extrema this way, fractal activity-based cycles were defined then as the period between two consecutive local maxima of the normalized and smoothed spectral slope series.

### 3.2.3 Statistical analysis

Non-parametric tests were used as the normality assumption of the classical and fractal cycle durations did not hold. Spearman's correlations were assessed between the classical and fractal cycle durations for each dataset separately and for the pooled data as well.

The number of cycles detected by the two methods didn't always match, the mean number of the classical cycles was 4.7 ± 0.9, for the fractal cycles 4.6 ± 1.0 cycle per night, while the prevalence of cycle number mismatch was 34-55%, depending on dataset. In the cases where cycle numbers were equal between the two methods, the durations of corresponding cycles were correlated. In case of cycle number difference between the methods, the cycle durations were averaged per participant and the average classical and fractal cycle durations were correlated.

Comparisons were made between the pediatric and young adult groups, MDD patients and controls, MDD patients with REM-suppressive versus REM-non-suppressive antidepressent treatments. Paired samples tests was applied to compare medicated and unmedicated states in MDD.

# 4 Results

## 4.1 Study 1 - Scale-free and oscillatory spectral measures of sleep stages in humans

### 4.1.1 Spectral slope

The spectral slope of the EEG showed a strong main effect of sleep stage, see Figure 2 [$F_{(4,824)} = 770.29, p < 10^{-5}, \eta_p^2 =$

0.788], with highest slope values (flattest PSDs) during wakefulness, then decreasing throughout non-REM sleep, reaching the lowest values (steepest spectral slopes) in slow wave (N3) sleep, and increased again in the REM stage. Age group also showed a significant main effect, revealing a general flattening of the EEG spectrum in sleep with the progression of age [$F_{(3,206)} = 6.47, p < 10^{-4}, \eta_p^2 = 0.086$] and stage-region-age effect [$F_{(48,32)} = 4.95, p < 10^{-5}, \eta_p^2 = 0.067$], see Figure 2, where flattening of the spectral slope in SWS with aging can be noted, indicating the deterioration of sleep quality in older subjects.

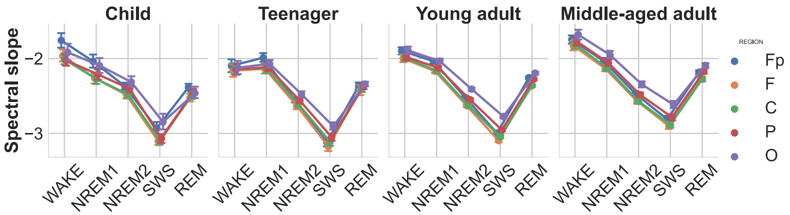

Figure 2: Spectral slopes as functions of sleep stage, brain region, and age group. Note the gradual decrease of slope values (decreasing spectral exponents, increasing steepness) during the course of deepening of NREM sleep, as well as a relatively increased slope in REM sleep (but still below the NREM1 values). Vertical bars denote 95% confidence intervals.

### 4.1.2 Central peak frequency

Observing the central frequency of the dominant peak, a strong main effect of brain region was revealed [$F_{(4,824)} = 58.138, p < 10^{-5}, \eta_p^2 = 0.22$], with increased frequencies in the frontal and frontopolar derivations. Significant effects of age [$F_{(3,206)} = 17.2, p < 10^{-5}, \eta_p^2 = 0.2$] and sleep stage [$F_{(4,8)} = 15.584, p < 10^{-5}, \eta_p^2 = 0.07$] were found, the peak frequencies converging to sleep spindle frequencies in the non-REM stages.

### 4.1.3 Peak power

The power of the dominant spectral peak also was significantly different between sleep stages [$F_{(4,824)} = 88.765, p < 10^{-5}, \eta_p^2 = 0.301$] and brain regions [$F_{(4,824)} = 97.645, p < 10^{-5}, \eta_p^2 = 0.321$]. It is worth to note the inverted U-shape of peak power with aging in NREM2 sleep, being most prominent in teenagers and young adults, yet diminished in children and middle-aged adults.

## 4.2 Study 2 - Fractal cycles of sleep, a new aperiodic activity-based definition of sleep cycles

### 4.2.1 Fractal cycles in healthy adults

Upon simple quantified inspection, known features of sleep were instantly revealed in the spectral slope series. More specifically that the slope alternated between peak-trough-peak 4-6 times during a night, and the duration of a cycle was around 90 minutes. The pooled average across cycles in all datasets of the fractal cycle duration was $89 \pm 34$ min, while for classical cycles $90 \pm 25$ min. Correlations between the per participant averaged durations of classical and fractal cycles were significant in all six datasets ($r = 0.4$–$0.5$).

### 4.2.2 Correspondence between fractal and classical cycles

The timings and durations of fractal cycles matched classical cycles in 81% of cases, 763 out of 940 cycles in all datasets. The fractal and classical cycles were overlapping in 54% of all participants (111 out of 205), $r = 0.5 - 0.8, p < 0.001$. In participants with fractal and classical cycle number mismatch, the average cycle number difference (fractal-classical) was $-0.23 \pm 1.23$ cycles, ranged between -2 and 2, in these cases lower correlations were found between the cycle numbers ($r = 0.28, p = 0.006$) and cycle durations ($r = 0.278, p = 0.006$).

### 4.2.3 Fractal cycles and age

In the following, a child group (n=21, Dataset 6) in the age range of 8-17 years (mean: $12.4 \pm 3.1$ years) was compared to young adult participants selected from the rest of the datasets (n=24) in the age range of 23-25 years (mean:

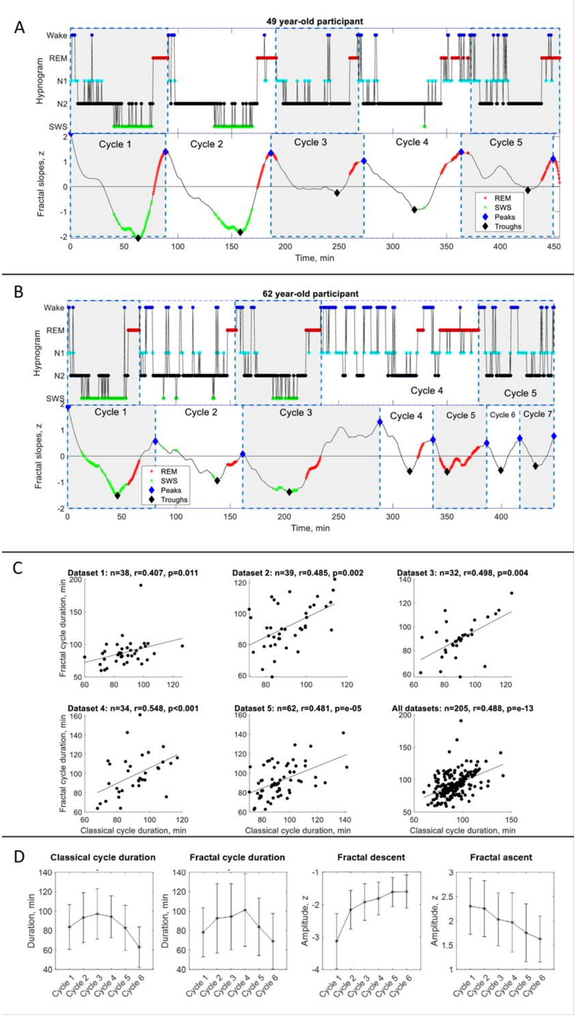

Figure 3: Fractal cycles in healthy adults, cycle turning points are the local maxima of the spectral slope series. Examples of **A)** matching and **B)** mismatching classical and fractal cycles. **C)** Correlation of average cycle durations per participant. **D)** Cycle-to-cycle dynamics of cycle durations, fractal descents and ascents.

$24.8 \pm 0.9$ years).

Children manifested significantly shorter fractal cycle durations of $76 \pm 34$ min, while for young adults cycles were around $94 \pm 32$ min ($p < 0.001$, Cohen's d=-0.57), there was a similar difference in the classical cycles as well with $80 \pm 23$ min in children and $90 \pm 22$ min in young adults ($p < 0.001$, Cohen's d=-0.42).

The effect of age on sleep cycle duration was also investigated in the pooled healthy adult dataset in the age range of 18-75 years (mean:33.5 years). A reduction of mean fractal cycle duration was associated with the progression of age (r=-0.19, $p = 0.006$).

### 4.2.4 Fractal cycles in MDD

Fractal cycle durations were compared between healthy controls and patients with major depressive disorder (MDD).

An increase in fractal cycle duration was found in both short- and long-term medicated MDD patients relative to controls. Dataset 1 included long-term medicated patients, their fractal cycle durations were significantly longer ($97 \pm 43$ min) than those of healthy controls ($84 \pm 35$ min, $p = 0.001$, Cohen's d=0.3). In Dataset 3 a significant slowing of fractal cycles was present after 7 days of medication ($107 \pm 48$ min, $p < 0.001$, Cohen's d=0.5) and persisted after 28 days ($106 \pm 51$ min, $p = 0.001$, Cohen's d=0.4) when compared to the baseline unmedicated states of the same individuals ($88 \pm 32$

min).

Antidepressant medication type was also and important factor when comparing cycles of MDD patients. Fractal cycles in patients taking REM-suppressants were significantly longer ($95 \pm 44$ min, $p = 0.003$, Cohen's d=0.5) than in those under REM-non-suppressive treatment ($121 \pm 55$ min). Differences between healthy controls and unmedicated MDD patients were non-significant.

# 5 Conclusions

Based on the results presented in the previous sections the following conclusions could be drawn:

- Aperiodic neural activity carries meaningful information about brain states in sleep, more precisely the spectral slope of the EEG is distinct in each sleep stage, thus a reliable indicator of objective sleep depth.
- As the overnight dynamics of the spectral slope reflected sleep architecture, it was possible to construct a mathematically formulated definition of sleep cycles based on the fractal activity.
- Fractal cycle length and timing coincided with manually annotated classical cycles in the majority of cases, furthermore it could detect cycles with of skipped or interrupted REM sleep.

- Known effects of aging on sleep were identified both in the aperiodic and oscillatory spectral parameters. Flattened spectral slopes reflected the shallowing of sleep with the progression of age, fractal cycle length increased in children and decreased in adults with age, peak power corresponding to spindle activity also followed an inverted U-curve, being maximal around the age of maturation.

- Having observed that fractal cycle durations were significantly increased in medicated patients with major depressive disorder, suggests the method could as a tool in the analysis of the effects of antidepressants on sleep, and potentially other clinical settings.

# 6 Bibliography of the candidate

## 6.1 Publications of the thesis

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