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Potential dementia biomarkers based on the time-varying microstructure of sleep EEG spindles

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Abstract— The time-varying microstructure of sleep EEG spindles may have clinical significance in dementia studies. In this work, the sleep spindle is modeled as an AM-FM signal and parameterized in terms of six parameters, three quantifying the instantaneous envelope (IE) and three quantifying the instantaneous frequency (IF) of the spindle model. The IE and IF waveforms of sleep spindles from patients with dementia and normal controls were estimated using the time-frequency technique of Complex Demodulation (CD). Sinusoidal curve-fitting using a matching pursuit (MP) approach was applied to the IE and IF waveforms for the estimation of the six model parameters. Specific differences were found in sleep spindle instantaneous frequency dynamics between spindles from dementia subjects and spindles from controls.

I. INTRODUCTION

THE sleep spindle waveform is a transient event of human stage 2 sleep electroencephalogram (EEG). It is defined as a group of rhythmic waves within the frequency range of 11-15 Hz, exhibiting a progressively increasing, then gradually decreasing, amplitude. It is usually of 0.5-2 sec duration, and it may be present in low-voltage background EEG, or superimposed on delta EEG activity, or temporally locked to a K complex [1]. There is evidence that sleep spindles are generated by cortico-thalamo-cortical neuronal networks, and they are hypothesized to play an active role in inducing and maintaining sleep [2]. They are affected by cerebral impairment [3]. Accordingly, in neurodegenerative disorders leading to dementia they may become less numerous, and their morphology appears to deteriorate significantly [4].

This work presents preliminary results on the use of six parameters, quantifying the time-varying microstructure of sleep spindles, as EEG-based biomarkers in dementia.

II. METHODS

A. Model for a Sleep Spindle

Sleep spindles can be modeled as AM-FM signals and can be expressed as [5]:

$$f(t) = A(t)\cos[g(t)]; A(t) \ge 0 \qquad (1)$$

where, $A(t) = A_0 + k_a \cos(2\pi f_a t + \theta_a)$, as a simple approximation, is a model for the instantaneous envelope (IE), and $g(t) = 2\pi f_0 t + k_b \cos(2\pi f_b t + \theta_b)$, as a simple approximation, is a model for the instantaneous phase [6]. The instantaneous frequency (IF), in rads/sec, is the time derivative of $g(t)$. Figure 1a shows an example of the above model (simulation), while Fig. 1b shows a real sleep spindle. Observe that the time-varying morphology of the real spindle justifies the chosen model. According to the assumed neurophysiological mechanisms for sleep spindle generation [2,7], one may hypothesize that $A(t)$ and its defining parameters (A_0, k_a, f_a) model primarily cortical processes, while $g(t)$ and its defining parameters (f_0, k_b, f_b) model primarily thalamic processes.

The model in Equation (1) was assumed in this work. Since sleep spindle morphology appears to deteriorate in dementia, and dementia may be viewed as a result of cortical or sub-cortical pathology [4], the hypothesis can be made that this change in spindle morphology could be reflected in the model parameters.

B. Estimation of IE and IF Waveforms

Previous work has compared several time-frequency methods for the estimation of IE and IF waveforms [8, 9]. Accordingly, methods based on the Hilbert transform (HT), Complex Demodulation (CD), Matching Pursuit (MP) and Wavelet transform (WT) were analyzed and compared as to their efficacy in estimating the six parameters (A_0, f_a, f_0, k_b, f_b) of the proposed AM-FM model for a sleep spindle. CD was found to exhibit a good compromise between signal distortion (about 0.24 sec for a 512 Hz sampling rate) and estimation error for the parameters (less than 10% in simulated data). Due to the above reasons, CD was used in this study.

Before applying CD, the spindle data were filtered through a band-pass, zero-phase, FIR filter of order 128, with frequency cut-offs at 5 and 22 Hz. The cut-offs were chosen such that the spindle waveform components in the

pass-band of 11-15 Hz were passed with unity gain.

The procedure of applying CD to a given sleep spindle signal was as follows [5]:

(1) The frequency spectrum of the signal was shifted to the left (towards the origin) by the demodulating frequency, which was taken to be the "center of gravity" of the Fourier transform of the signal in the frequency band of 9.5-16.5 Hz, where most of the energy of a sleep spindle lies.

(2) The resulting complex signal was filtered with a low-pass, zero-phase, FIR filter, of order 100, having a cut-off frequency of 6 Hz. This cut-off frequency was chosen based on simulations and real spindle data which indicated that, beyond that frequency, the frequency content of the spindles may be considered negligible.

(3) The frequency spectrum of the filter output was shifted to the right by the demodulating frequency.

The instantaneous envelope and phase (as well as frequency) functions of the spindle signal were subsequently calculated from the magnitude and argument, respectively, of the complex function that resulted after the last step. Thus, we obtained the IE and IF waveforms. As mentioned above, for a sampling rate of 512 Hz used in this work,

(a)

(b)

Fig. 1: Simulated sleep spindle (a) produced with the model of Eq 1, and real sleep spindle (b) after band-pass filtering (5-22Hz).

about 0.24 sec of data had to be deleted from the estimated waveforms because of the distortion introduced by the CD method (due to the low-pass filtering).

C. Model Parameter Estimation

Since the estimated IE and IF waveforms may not be purely sinusoidal, MP-based curve-fitting was performed in order to estimate the six parameters that define the spindle model. In MP, the aim is to decompose a given signal S into a linear combination of N waveforms (atoms) d_i chosen from a predefined dictionary D_k so that:

$$S = \sum_{i=1}^{N} w_i d_i + R_N \qquad (2)$$

where, R_N is the decomposition residual. In this work, the decomposition was performed only once, i.e., for the first d_i atom chosen by the method. Accordingly, for each IE and IF waveform, one atom was chosen from the following dictionary

$$D_{fit} = \cos\left(2\pi f_{fit} t + \phi_{fit}\right) \qquad (3)$$

where, $f_{fit} = 0.1{:}0.005{:}6$ and $\phi_{fit} = 0 : \dfrac{\pi}{10} : 2\pi$.

The six model parameters were then estimated from the MP-fitted sinusoids. Specifically, f_a and f_b were obtained directly from the sinusoid dictionary created within the MP procedure. The remaining four parameters were estimated from maximum and minimum values of the IE and IF waveform-adjusted sinusoids.

D. Sleep Spindle Data

Night sleep EEG signals from 3 healthy young adults and from 3 subjects with dementia were obtained from the Sleep Research Unit of the Department of Psychiatry at the University of Athens. Standard sleep recording procedures were applied for the sleep EEG recordings, utilizing a Brain Spy (Micromed) data acquisition system at 512 Hz sampling rate. Data from the second or third recording night of the subjects were used in this study. The dementia subjects were drug-naïve in-patients at the Neurological Clinic of the University of Athens and were diagnosed for dementia through standard neuropsychological procedures. The dementia cases had different etiologies, including progressive supranuclear palsy (female, 59 yrs), posterior cortical atrophy (female, 68 yrs) and fronto-temporal dementia, semantic type (male, 71 yrs).

The whole night sleep EEG record of each subject was visually scored for sleep stages according to standard procedures [1]. Each record was divided into three parts of equal length, and visually well-defined sleep spindles from the largest sleep stage 2 of each part (3-4 spindles) were obtained for automatic analysis.
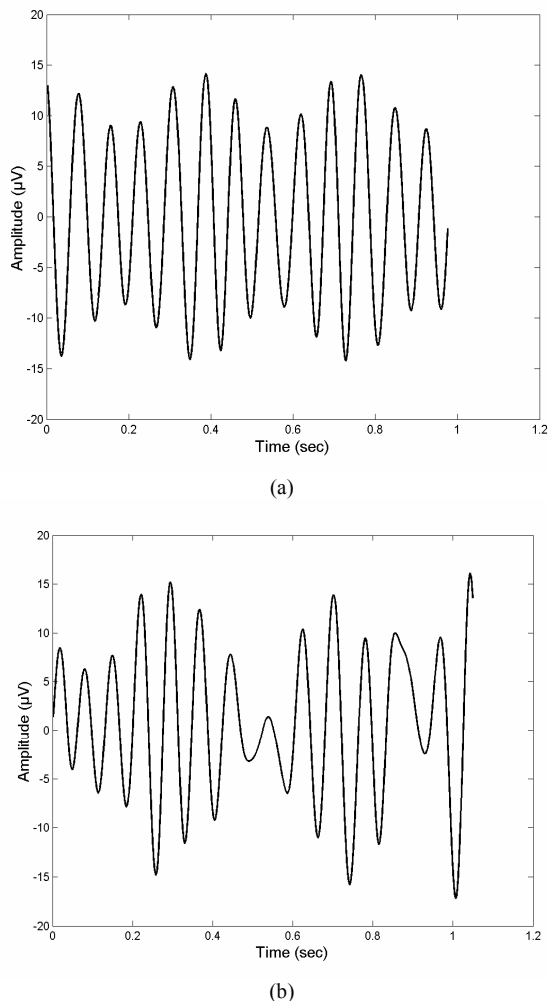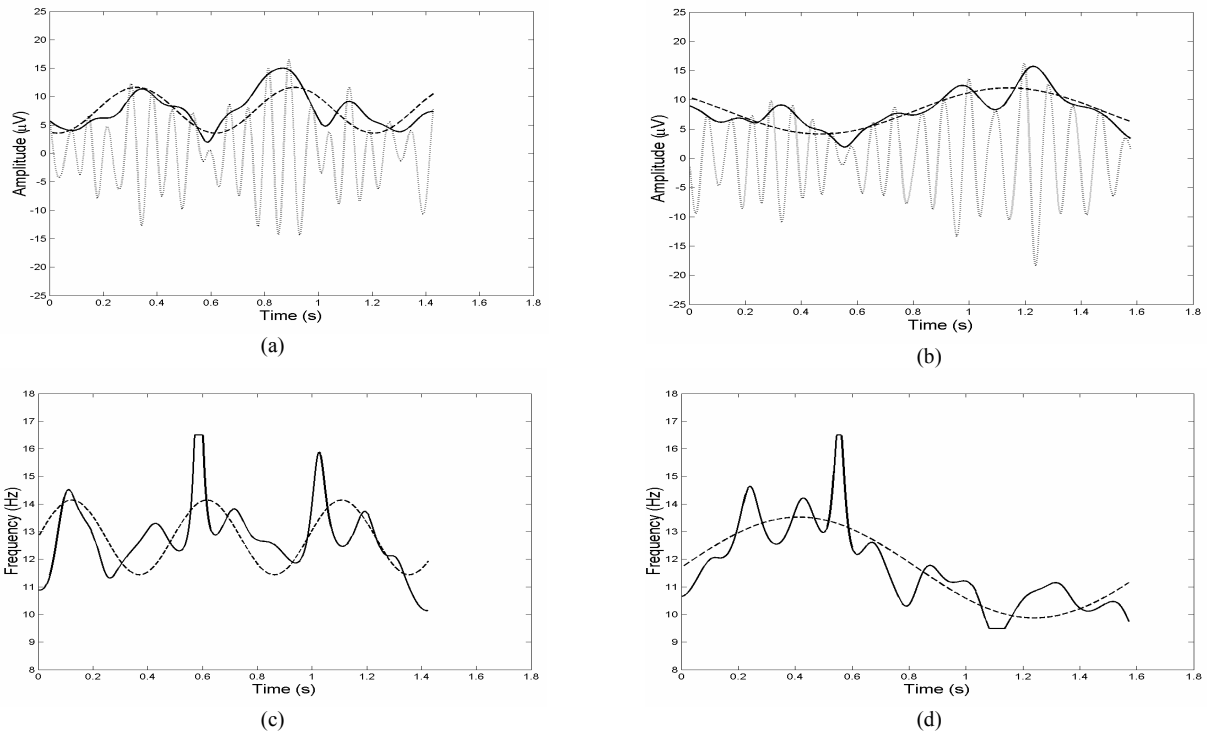
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Fig. 2. Two examples of sleep spindles and related IE and IF waveforms and MP-fitted curves in control subjects. (a), (b) spindles, IE waveforms and MP-fitted curves. (c), (d) IF waveforms and MP-fitted curves. Solid lines correspond to CD-estimated IE and IF waveforms and dotted lines correspond to MP-fitted curves.
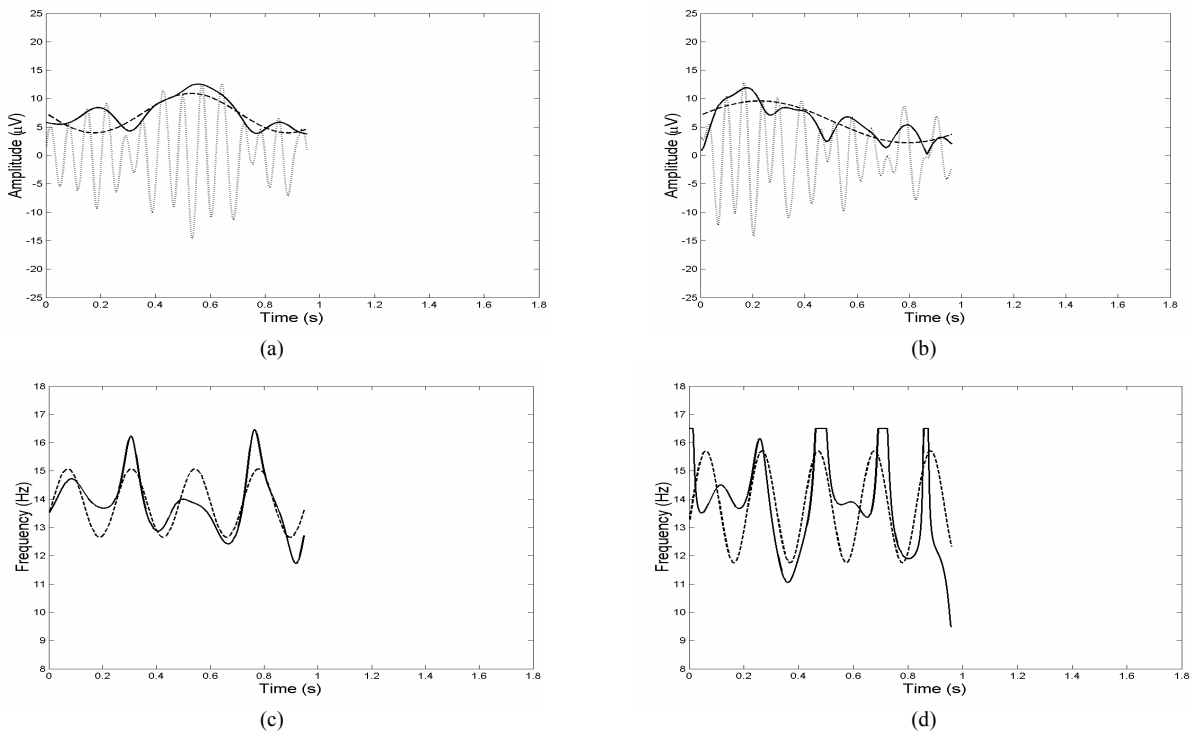

Fig. 3. Two examples of sleep spindles and related IE and IF waveforms and MP-fitted curves in dementia subjects. (a), (b) spindles, IE waveforms and MP-fitted curves. (c), (d) IF waveforms and MP-fitted curves. Solid lines correspond to CD-estimated IE and IF waveforms and dotted lines correspond to MP-fitted curves.

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	Controls (n=11)	Dementia (n=11)
A_0 (microvolts)	8.50±1.98	7.62±2.48
f_a (Hz)	1.01±0.59	1.35±1.00
k_a (microvolts)	5.23±2.11	5.82±3.44
f_0 (Hz)	12.55±0.57	12.63±1.20
f_b (Hz)	1.55±1.15	3.23±1.40*
k_b (rads)	1.48±1.20	0.82±0.84
Duration (sec)	1.90±0.73	1.33±0.27*

III. RESULTS

Sleep spindles exhibiting well-defined, quasi-sinusoidal IE and IF waveforms were chosen for further analysis and parameter estimation. As a result, 11 spindles from controls and 11 spindles from dementia subjects were chosen for parameter estimation.

Spindles from dementia subjects were less well-defined visually and appeared shorter than spindles from controls. However, any detail as to modulation patterns in instantaneous envelope and instantaneous frequency was not easily discernible visually. Figure 2 shows two spindle examples, each one from a different control subject, while Figure 3 shows two spindle examples, each one from a different dementia subject. As shown, the spindles from the dementia subjects are shorter and less well-formed than the spindles from the controls. In addition, the spindles from the dementia subjects exhibit faster oscillations in the sinusoids fitted to the IF waveforms (related to f_b) than the spindles from the controls.

Table 1 shows average values for model parameters and spindle duration across all spindles analyzed in this work. As expected from Figs. 2 and 3, the dementia subjects differed significantly from controls as far as f_b and spindle duration was concerned.

IV. DISCUSSION AND CONCLUSION

The results presented in this work indicate that the proposed sleep spindle parameterization may quantify subtle differences in the time-varying microstructure of sleep spindles which are not that obvious visually. These differences may have clinical significance. Sleep spindles from dementia subjects were found to exhibit faster instantaneous frequency dynamics, quantified by parameter f_b, than spindles from controls. This finding, coupled to the shorter spindle duration, may relate to the visually obtained impression that sleep spindles in dementia exhibit a "deteriorated" morphology. Therefore, the proposed spindle

model parameters appear promising as potential EEG-based biomarkers in dementia. However, additional studies, involving larger data sets, are needed to explore this promise further. In particular, future work should investigate the possibility that the IF waveform parameters reflect dynamics at the thalamic site(s) responsible for sleep spindle generation [2, 3, 7], which may be compromised as a result of brain pathology in dementia.

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