EEG-Based Brain Connectivity Analysis of States of Unawareness

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Abstract— **This work investigates phase synchrony as a neuro-marker for the identification of two brain states: coma and quasi-brain-death. Scalp electroencephalography (EEG) data of 34 patients were recorded in an intensive care unit (ICU), with 17 recordings for patients in a coma state, and 17 recordings for patients in a quasi-brain-death state. Phase synchrony was used for feature extraction from EEG recording by comparing the phase value between pairs of electrodes using an entropy based measure. In particular, we performed phase synchrony analysis in five standard frequency bands and provide visualization of the phase synchronies in matrices. The effectiveness of the phase synchrony features in each of the frequency bands are evaluated with statistical analysis. Results suggest phase synchrony for coma patients has a significant increase in the theta / alpha band compared to quasi-brain-death patients. Hence, we propose phase synchrony as a candidate for the identification of consciousness states between coma and quasi-brain-death.**

I. INTRODUCTION

The ability to find robust neuro-markers to quantitavely evaluate the level of consciousness will increase our understanding of the human brain in general. In particular, for medical applications, such a neuro-marker would provide valuable information to doctors for diagnosis, especially considering the ethical and legal aspects involved. The Electroencephalogram (EEG), as one of the means of brain data measurement, is non-invasive and has a high temporal resolution. Among all brain imaging techniques, EEG is widely used in applications where changes in time are important, such as the ongoing monitoring of brain states. Intensive Care Units (ICUs) are widely equiped with EEG devices to monitor patients' brain states. Although it is standard practice for specialized personnel to examine a patient's brain state, it is not feasible to position such specialists to monitor one single patient 24 hours a day, 7 days a week. Thus, it would be of great benefit to be able to provide a tool that can continuously monitor patients' brain states to automatically identify changes and to alert clinical doctors for emergency treatment. From the legal point of view, brain death is defined as an irreversible loss of forebrain and brainstem functions, but implementing brain death diagnosis precisely is challenging, mostly due to clinical difficulties. The diagnosis process for brain death varies from country to country, but all require repeated clinical testing. If a patient is diagnosized as quasi-brain-dead (QBD), the patient might need to be disconnected from important medical care (i.e. the respirator) and transported out of the ICU temporarily to perform further diagnosis tests before the patient is finally confirmed as brain dead. This might stress the already compromised organs. Extra care should be taken before moving patients out of ICU. A robust neuro-marker with physical meaning would help this process, serving as a pre confirmation tool to doctor's final decision to disconnect patients from vital clinical support

Among neuro-markers for cognitive studies, phase synchrony has been regarded as a method to probe large scale integration in the brain. Synchrony results from the firing at the same rate of thousands of pyramidal cells, organized in cortical columns. The question is how these synchronies in the brain are related with consciousness. Initial experiments were done on the rabbit's olfactory bulb [1] to correlate the synchrony of simultaneously firing cells with the presence of specific odors. More than 10 years later, Gray and Singer [2] showed that local synchrony between two neurons results from specific stimulus presentation patterns. Recording activity in the visual cortex of cats, a local group of neurons fired synchronously at $40Hz$ upon stimulus presentation. This periodic neuronal activity correlated with the orientation of the stimulus, showing that the emergence of a distinctive sensory response could be due to the synchrony of a local neuron assembly firing together. To extrapolate this idea to a more large-scale synchrony in the brain, beyond the local field recording [2], macroelectrodes could be used in a more broad scale between different cortical areas. The main idea is to observe the phase response to target stimuli [3], which leads to a synchronisation between long-range areas [4] relative to a specific cognitive activity (i.e. a relevant visual stimulus). In our study, we focus on the synchrony in different frequency bands between pairs of electrodes during "resting" coma and quasi-brain-death state. Then the phase synchronies among electrodes, is represented in a matrix for each of the frequency bands. The effectiveness of the phase synchrony is evaluated and reported via statistical analysis.

II. SENSING - DATA ACQUISITION

The EEG data were recorded in an intensive care unit (ICU) using the standardized 10-20 system in HuaShan Hospital, Shanghai, China. The EEG acquisition device was a portable NEUROSCAN ESI system. Given the fact that all patients were lying on the back with head up, EEG electrodes were attached to the scalp on the frontal aspect of the head. Nine electrodes were used for recording. Among them, two electrodes were positionned on the ears (left and right) as reference (A1, A2). Other electrodes (Fp1, Fp2, F3, F4, F7,

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F8, Cz) were used for data acquisition, with Cz being the ground electrode. The corresponding channel numbers for the electrodes were: Fp1 - channel 1, Fp2 - channel 2, F3 - channel 3, F4 - channel 4, F7 - channel 5, F8 - channel 6. The sampling rate of the recording was set at 1000 Hz. 34 patients were recorded, 16 males and 18 females, with an age range from 17 years old to 85 years old. 17 subjects were recorded for each category of patient: 17 patients in coma and 17 patients in Quasi-Brain-Death (QBD). All the patients were examined by two independant physicians for the coma test, pupils test and brainstem reflexes. We measured the EEG at this stage.

III. FEATURE EXTRACTION

The proposed method uses two successive steps to obtain phase synchrony between pairs of electrodes. First, for each channel of the EEG recording, phase features were extracted. The second step is to calculate a Phase Synchrony Index (PSI) between each pair of electrodes. Algorithms for estimating the phase synchrony feature are described in this section.

A. Phase Estimation for Each Channel of Data

Phase estimation has been well developed mainly in two ways. One way follows the work of the LENA group in France [5] [6] using the wavelet convolution of a filtred signal in a narrow band and research from the German group [7] using an Hilbert transform. The aim is to differentiate the temporal signal $x(t)$ to a complex one, which carries both amplitude and phase information as: $a(t)e^{(j2\pi f(t)+\theta(t))}$, where $a(t)$ carries the envelope of the signal, and the phase is retrieved by $\theta(t)$. Phase estimation using the above mentioned two methods were compared and no significant difference was found. It should be noted that the phase can also be estimated with Short Time Fourier Transform (SFFT), but it is not suitable to be applied on EEG data due to the non-stationarity of EEG signals. In our study, we used the established method in [5]. This method does not require computation in the complex domain and is suitable for real-time analysis as the complexity of computation is low. The process is:

- Step 1: Apply band pass filter to the data.
- Step 2: Extract the local maxima M_i as an index vector of maxima for each of the band passed data using first derivative.
- Step 3: For each local maxima, compare the time shift from an ideal signal at the frequency of interest.
- Step 4: A value of phase is obtained from the time shift of maxima.
- Step 5: Construct a signal of phase changes over time.

In our analysis, we focus on the different frequency bands of signals. A Finite Response Filter with order 100 (101 samples of data) was used to perform filtering. A frequency band of 0-4Hz is used for Delta, 4-6Hz for Theta, 8-12Hz for alpha, 18-22 for beta and 28-30Hz for Gamma. Next, we computed the relative phase compared to an ideal signal at the frequency of interest. The phase information is then estimated by:

$$\theta = (M_i \ mod \ \frac{F_e}{F_f}) * \frac{F_f}{F_e} * 2 * \pi, \tag{1}$$

where mod is the modulus operator, F_e and F_f are respectively the sampling frequency of the signal and the frequency of interest and M_i, the ith local maxima. After the relative phase was computed for each local maxima, the phase of the signal along the time is reconstructed by interpolation.

B. Quantifying Phase Synchrony via Phase Synchrony Index

Different terms are used to define phase relationships, i.e. “in phase”, “out of phase”, “phase locking”. We follow “phase locking” defined in [6] for phase synchrony estimation, measuring phase locking instead of phase-amplitude coupling. That is, for signals $s_1(t)$, $s_2(t)$, and their corresponding phases $\phi_1(t)$, $\phi_2(t)$,

$$\phi_{12}(t) = |n\phi_1(t) - m\phi_2(t)| \tag{2}$$

where n, m are integers indicating the ratios of possible frequency. We focus on the case $n = m = 1$ for this application. If $\phi_{12}(t)$ is a constant, it means that the events detected by two individual electrodes are phase locked, therefore indicating there is an interaction within the brain.

Having obtained phase information from the data, phase synchrony is quantified by an entropy-based method as described below. The phase difference between the two observed signals is given by $\phi_{ij}(t)$, for the electrodes i and j. In order to statistically quantify the phase synchrony, an index is used to indicate the degree of phase synchrony, ie. the PSI. It can be quantified using Shannon entropy by the phase coherence value (PCV) [7], [8]:

$$\rho_{ij}(t) = \frac{E_{max} - E}{E_{max}} \tag{3}$$

where $E = -\sum_{n=1}^{N} p_n \ln p_n$, Shannon's entropy of $\phi_{ij}(t)$, is calculated using time window $(t : t + W)$, with W being the window length. N is the number of phase bins, whereas p_n is the probability of ϕ_{ij} being obtained within time window $(t : t + W)$. The best suitable number of bins N is calculated from $N = \exp(0.626 + 0.4 \ln(W - 1))$, and $E_{max} = ln(N)$. In this way, phase synchrony varies between 0 and 1, with 1 being perfect synchrony, and 0 being out of phase.

IV. RESULTS

The effectiveness of the method for phase synchrony extraction is demonstrated using two synthetic signals. Then analysis results on data from 34 patients are presented. The level of synchrony among pairs of electrodes recorded from EEG signals are shown in matrices for coma and quasi-brain-death subjects respectively. In addition, statistical analysis is performed to evaluate the effect.

A. Phase synchrony analysis on synthetic signals

Our phase synchrony approach is first demonstrated on two synthetic signals, as shown in Fig. 1, where the top

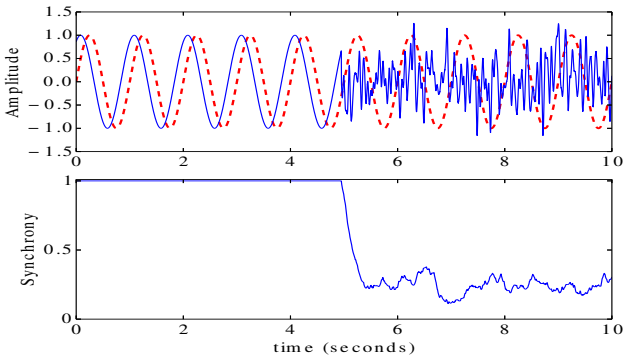


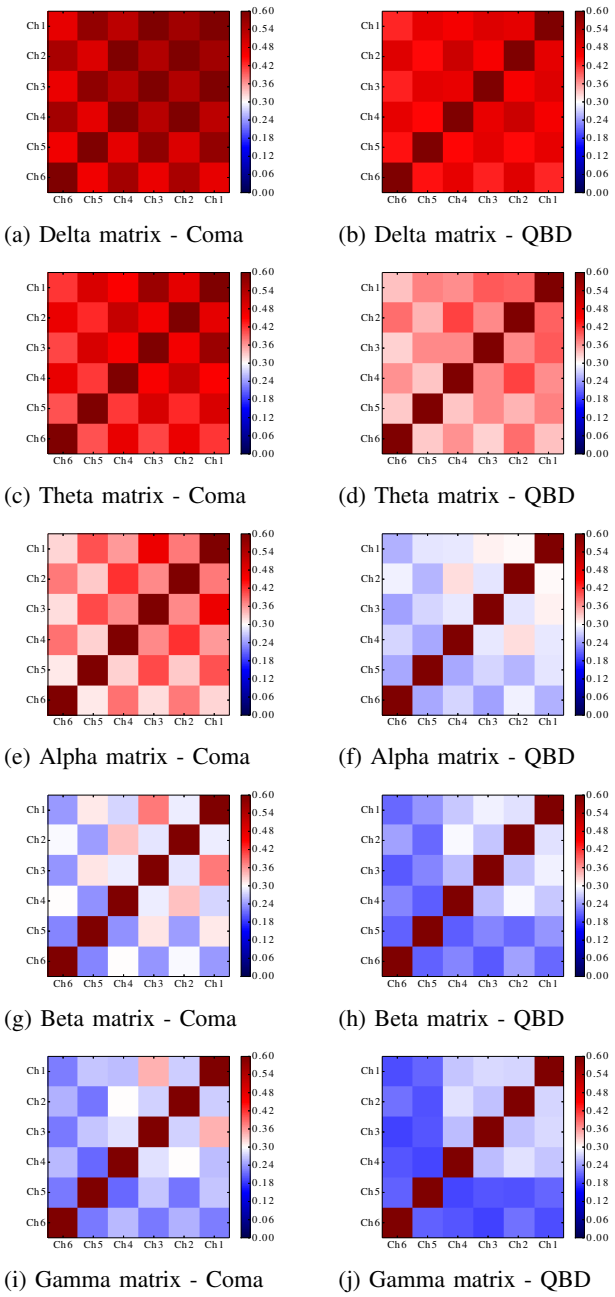
Fig. 1. Phase synchrony analysis on synthetic signals. Top panel: $S2$ phase changes with time, bottom panel: phase synchrony index computed between $S1$ and $S2$.

panel shows two signals. Signal $S1 = sin(wt)$, shown in red dotted line, is a sinewave of 10 seconds. Signal $S2$, shown in solid blue line, is plotted using $S2 = sin(wt + \phi(t))$ with $\phi(t)$ being $\pi/3$ for the first 5 seconds. From 5 seconds onwards, the phase for $S2$ changes randomly. Phase synchrony for each time point was calculated using a sliding window. As shown in the bottom panel of Fig. 1, phase synchrony index is 1 for the first 5 seconds, indicating perfect synchrony/phase locking of $S1$ and $S2$. From 5 seconds onwards, $S1$ and $S2$ are out of phase, shown in the figure as reduced synchrony. As expected, there is higher synchony when the two phases are locked, but reduced synchrony when phase of one signal shifts away from the other.

B. Results - Phase synchrony matrices

The Phase Synchrony Index (PSI) was estimated for each pair of electrodes (15 combinations), with a non-overlapping window of a length of 1 second ($W = 1000$). For each pair of electrodes we obtain a PSI for each non-overlapping window. Then we calculated the mean by averaging PSI across all the windows. This mean is shown in Fig. 2 with blue being a lower synchrony, red being a higher synchrony. The maximum synchrony detected is below 0.6, so the color range scale is between 0 and 0.6. The matrices were plotted in two columns and five rows. The first column shows the matrices of mean phase synchrony for all pairs of electrodes across all coma patients. The second column shows the matrices for all QBD patients. The matrices in each row indicate the phase synchrony for each frequency band (from top to bottom: Delta, Theta, Alpha, Beta, Gamma). Each element in a matrix represents the PSI between a pair of electrodes. For each matrix, the diagonal from the bottom left corner to the upper right corner indicates the relationship to itself, thus the synchrony (PSI) for all diagonal elements are 1 (perfect synchrony). Each non-diagonal element in a matrix indicates the PSI between two different electrodes. For example, the top left corner element in a matrix indicates the PSI between row 1 (channel 1) and column 1 (channel 6).

The results are interpreted by the physical meaning of phase synchrony/locking: in chaos theory, the process of phase locking occurs whenever the chaotic actions of the



(a) Delta matrix - Coma (b) Delta matrix - QBD

(c) Theta matrix - Coma (d) Theta matrix - QBD

(e) Alpha matrix - Coma (f) Alpha matrix - QBD

(g) Beta matrix - Coma (h) Beta matrix - QBD

(i) Gamma matrix - Coma (j) Gamma matrix - QBD

Fig. 2. Phase Synchrony Matrix: Coma vs QBD

individual shift to the ordered actions of a collective system [9]. This gives a fundamental background to why phase synchrony is important for understanding neuron integration, especially why it is particularly useful for the identification of coma and quasi-brain-death. Coma patients have the ability to shift individual chaotic actions to the ordered actions of a collective system. The "chaotic to ordered" process is reflected by phase synchrony, whereas brain death patients do not have the ability to conduct cognitive operations, therefore, phase synchrony for coma patients should be higher than that of QBD. The analysis results suggest the mean PSI for coma data, as shown in the matrices, is higher than in QBD.

C. Statistical Analysis

To further investigate the effectiveness of the phase synchrony feature, we performed a statistical test (2-sample independant t-test) to compare the PSI between coma and QBD for every electrode pair available in each frequency band. The significance threshold set to reject null hypotheses was 0.05. Moreover, Bonferroni correction was performed to correct from multiple comparisons. Thus the significance threshold was corrected to 0.0033. This was set by dividing p-values with 15, as the number of statistical comparisions is 15 (pairs of connections) for each frequency band. Results suggest all electrode pairs at Alpha or Theta bands are significant after correction, whereas only nine electrode pairs are significant in the Delta band. Beta band sees nine pairs of electrodes significant. For Gamma band, only one electrode pair is significant. The analysis is done by comparing the p-value for a 2-sample independent t-test with 0.0033. All electrode pairs in Theta or Alpha bands had p-values smaller than 0.0033 indicate the coma patients's phase synchrony are stronger in Theta or Alpha band than that in QBD.

We also performed a nonparametric permutation test with no assumptions on the distribution of the PSI. In theory, the multinomial coefficient states that there are $2.3336 \times 10^9 = 34!/(17! \times 17!)$ possible permutations. Empirically, 1,000 iterations are regarded as sufficient to build a high-signal-to-noise-ratio distribution, so we performed 10,000 iterations for our analysis to achieve robust results. The statistical test results suggest all electrode pairs are significant after correcting multiple comparison (p-value$<$0.0033) in the Theta or Alpha band, whereas only 10 pairs in the Delta band, 2 pairs in the Beta band, and 1 pair in the Gamma band were observed to be significant.

V. DISCUSSION AND CONCLUSION

Despite the low amplitude of the signal for patients in coma or quasi-brain-death states, these results suggest that patients in coma exhibit synchronisation in alpha, which confirms our previous study using a single pair of electrodes [10]. The novelty in this study rests upon consideration of all electrode pairs in all frequency bands. The strong synchrony over all pairs of electrodes suggests a global state of brain activity in coma patients. Another study [11] confirms indirectly our result: from coma to recovery, the highest synchrony is in the alpha band. Morever, there was a significant difference between coma and recovery. This suggests the brain during coma produces a large synchrony of alpha, which then reduces, either when the subject recovers from coma, where the usual brain function return, or when the brain goes into QBD. Furthermore, we find synchronisation in theta has a potential to differentiate coma and QBD patients as well. In addition, we found limited synchrony in QBD across all frequencies which suggests the brain is in its very last moment producing long range synchrony. It would be useful to pursue theses analyses on ageing subjects to understand the process from ageing to brain dead at their last span of life. Moreover, cerebral metabolism is null on brain death [12] but is reduced to about 40% in coma. So there is a larger difference in brain activity from QBD to coma, keeping in mind that cerebral activity in coma is close to that in deep sleep or general anesthesia, but for predicting between these different behavioural states, phase synchrony based EEG analysis has huge potential.

We have presented and demonstrated the potential of using phase synchrony for distinguishing between coma and QBD states. The results are very promising as a new tool to assist a pre-diagnostic test of brain death. Future work can be developed in building predictive models based on phase synchrony features for real-time monitoring. Predictive model building may be developed based on the significant elements in the matrices or combination of phase synchrony in different frequency bands. In addition, more recording should be acquired to be able to cross-validate the model and the method to provide a reliable tool for 'just in time' analysis to help clinical diagnosis.

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