CROSS-CORRELATION ANALYSIS OF EPILEPTIFORM PROPAGATION USING WAVELETS

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ABSTRACT -- We have analyzed cortical and subcortical field recordings from spatially distinct neural circuits in order to support the hypothesis that spatially distinct brain locations display correlated ictal activity during epileptic seizures. Field recordings have been obtained from cortex (CTX), anterior thalamic nuclei (AN), posterior thalamus (PT) and hippocampus (HPC) during pentylenetetrazol (PTZ) seizures in anesthetized animals. We use Wavelet Transform Cross-Correlation (WTCC) method in order to quantify the common activity between two recordings at particular bands of interest. In contrary to Fourier Transform Coherence (FTC), we show that WTCC provides a more reliable estimate of band-specific common activity or cross-coherence between two epileptic sources. Although most of the signal power is located at higher frequencies (15-30Hz), results from WTCC reveal significant mean cross-correlation estimates (~0.7-0.8) at primarily the lower regions of the spectrum (0-10Hz). The behavior observed in the brain recordings analyzed in this paper lets us differentiate between local and global behavior, where the global behavior is assumed to be due to a pacemaker function which is a quasi-periodic train of impulse functions that differentially excites various areas of the brain.

Index Terms – Cross-correlation analysis, epilepsy, propagation, wavelet analysis

I. INTRODUCTION

The studies of the network mechanisms of epilepsy over the last several decades has focused largely on the cerebral cortex, the hippocampus and the thalamus. The cerebral cortex and hippocampus have a natural inclination to generating large, synchronized bursts of activity underlying many forms of seizures due to strong recurrent excitatory connections, the presence of intrinsically burst-generating neurons, interactions among closely spaced neurons and synaptic plasticity [1]. The thalamus also plays a significant role in the potentiation of seizures [2].

Although the precise epileptic pathways underlying epileptic seizure activity remain largely unknown, some strong neural pathway evidence for a unique thalamocortical pathway is present. Through lesioning, autoradiographic, pharmacologic and electrical stimulation studies, Mirski et al. have discovered that the mammillothalamic tract and its associated nuclei specifically the anterior thalamus (AN) provide a propagation pathway during pentylenetetrazol (PTZ)-induced seizure activity. In addition to the physiological evidence, there have been varied uses of signal coherence in EEG studies for identification of affiliated brain centers during the seizure activity [3,4]. Sherman at al., using partial coherence estimation techniques, have shown significant coherence results between EEG signals recorded from AN and CTX. Both ordinary and partial coherence measures based upon the periodogram show statistical evidence in favor of a strong AN-CTX association [5].

In this study, we provide a different approach to confirm the interactions between spatially distinct brain centers and to be able to make the assumption of a globally propagating signal considered to be the underlying mechanism of the epileptiform activity observed at each brain recording. Our approach relies on coherence analysis using wavelets to verify that the brain centers where the field recordings are made have correlated and/or time-locked activity in accordance with the model shown in Fig. 1. Since our cross-coherence estimation method is based on wavelets, first we attempt to provide reasons for our choice of wavelets as opposed to Fourier transform by demonstrating the contrast between the cross-coherence estimation of two methods on real EEG data. Continuous Wavelet Transform (CWT), being a large set of band-pass filters, will allow us to focus on the time-locked components in order to establish a reliable cross-coherence estimation of two brain signals.

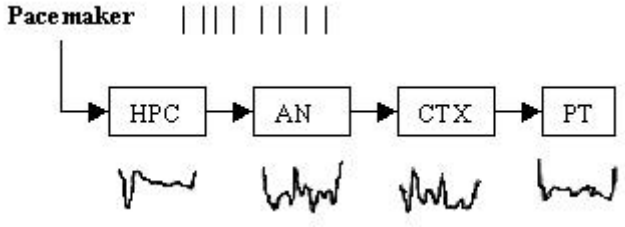

Figure 1. A systematic view of ictal discharge propagation mechanism. The pacemaker signal sequentially activates spatially distinct neural circuits. Each circuit produces characteristic impulse response in the field recording. The physiological properties and the current activity state of the underlying tissue determines the impulse morphology.

II. METHODS

The wavelet transform is a significant advancement in time-frequency analysis of signals such as EEG. It has certain advantages over Fourier transform techniques, since it does not require use of an infinite data window in dealing with sinusoids. Windowing is an important issue when dealing with signals similar to EEG that contain features that differ significantly in duration and frequency content over time.

There are reasons now to rely on wavelets for the estimation of cross-coherence across two brain centers. Here, we would like to define the cross-coherence between two signals as the band-specific cross-correlation. That is, by specific averaging in the frequency domain, we estimate the cross-correlation of specific range of oscillations. The proposed cross-coherence estimation approach is based on the assumption that two interacting brain centers display non-sinusoidal oscillations, e.g. time-localized spikes and waves. Superimposing spike-wave signal morphology on sinusoids, as in Fourier Transform, will unlikely reflect the actual frequency content, and therefore, the periodogram technique would not be a feasible alternative for cross-coherence estimation of brain recordings. On the other hand, the CWT allows us to enhance specific band of frequencies using signal reconstruction while achieving good time resolution in order to compute band-specific cross-correlation [6].

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Abstract

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A. Wavelet Analysis

We define the i^{th} band reconstructed signal defined in the continuous wavelet transform domain scale interval $(2^{i+1}-2^{i})$ as,

$$\Im_i(t)=\sum_{s=2^i}^{s=2^{i+1}}\frac{CWT_f(s,t)}{s} \quad \text{for i = 0,1,2, ..N} \qquad (1)$$

This is equivalent to dyadic decomposition of the function $f(t)\in L_2(\Re)$ into a total of N bands. The traditional frequency bands of interest in EEGs are shown in Table 1.

B. Cross Wavelet Transform

Wavelet transform of time domain cross-correlation of two signals is equivalent to cross-correlation of the wavelet transform of each signals.

$$WC_{gf}(a,b)=W_g f(a,b)=\frac{1}{c_\varphi}\iint W_\varphi f(s,\tau)\times W^*_\varphi g(\frac{s}{a},\frac{\tau-b}{a})\frac{ds d\tau}{s^2} \qquad (2)$$

Rather than computing cross-correlation functions in the CWT plane at every scale, we would like to perform a dyadic averaging of frequencies or signal reconstruction as in (1) and compute cross-correlations across the reconstructed signals from different sources. Then, at a particular band i, the cross-correlation function of two signals f and g is,

$$R_i(i)=\frac{1}{c}\int \Im_i(\tau)\Im^*_i(\tau+d)\,d\tau \qquad (3)$$

where d is the lag range.

The improved cross-correlation estimation can be attributed to the fact that wavelet transform with an appropriate scale can be considered an approximation of matched filtering, which extracts the deterministic signal and filters out noise and interference. The observed quasi-periodicity in the recorded brain signals suits this scenario very well. wavelet scales corresponding to consistent signal morphologies will enhance them in the continuous wavelet transform domain. By separating the signal into distinct bands of frequencies, we hope to increase the signal to noise ratio at particular bands to differentiate consistent signals from random fluctuations.

C. Cross Wavelet Coherence

At this moment, the i_{th} band time-varying wavelet coherence, $c_{f,g,i}(t)$, of $f(t)$ and $g(t)$ is

$$c_{f,g,i}(t)=\frac{\max\left(\frac{1}{2\Delta t}\int_{t-\Delta t}^{t+\Delta t}\Im_{f,i}(t+\tau)\Im_{g,i}(t+\tau+d)\right)}{\sqrt{\sigma^2_{\Im_{f,i}[t-\Delta t,t+\Delta t]}\cdot\sigma^2_{\Im_{f,i}[t-\Delta t,t+\Delta t]}}} \qquad (4)$$

As seen in the equation, a sliding window of length $2\Delta t$ ([-.4 ≤ d ≤ .4] sec) is applied throughout the signal period being analyzed.

Wave Number	Frequency Range	Band Symbol
8	0-4 Hz	δ
7	4-7 Hz	θ
6	7-15	α
5	16-31	β
4	31-63	γ
3	64-127	NA
2	128-255	NA

TABLE I. The traditional frequency bands are often specified as δ (less than 4 Hz), θ (4-7 Hz), α (7-15 Hz), β (15-31 Hz), and γ activity (above 31 Hz). There is much physiological and statistical evidence for the independence of several of these bands, but their boundaries can vary to some extent according to the particular experiment being considered and they can be adjusted as required.

Finally, we need to indicate the reasons of obtaining a time-varying coherence function and how we perform this operation. It is unreasonable to expect the same physiological behavior of the seizure activity to last for a long time. During an ictal discharge epoch lasting 8-10 secs, the dynamic behavior of the epileptic neural circuits may change in seconds [7]. Based on this assumption, we have developed an interest in a correlation function that would actually express the activity level of a seizure pathway connecting two brain structures at a chosen interval of time. For this purpose, we have applied a moving- average (MA) window to the CWT-reconstructed signals. The cross-coherence estimation inside each sliding window corresponds to one point in the correlation function of time. The sampling rate is 1000 Hz at each channel and the MA window is square and 800 points or 0.8 sec long. The window sliding speed is 50 points.

For the demonstration of the contrast between FFT and CWT coherence, we have used averaging windows of length 800 points in analyzing ictal discharge recordings of 4000 points long. The matlab 'cohere' function with Hamming analysis window of 256 points long and with sliding velocity of 50 points is used to estimate cross-coherence inside the averaging window. Then, frequency averaging is done to represent cross-coherence based on the frequency ranges shown in Table 1. Similar to wavelets, we obtain a time-varying cross-coherence function where each averaging window corresponds to a single point in the FFT-based cross-coherence function of time. Square averaging window of 800 points is used for wavelet coherence. We would like to note here that temporal resolution is achieved with the same analysis window in FFT. In wavelets, temporal resolution is already achieved by the specific morphology of the scaling function.

D. Experimental Setup

Male Sprague-Dawley rats (N=2) purchased from Charles River, Wilmington, MA, weighing 250-300 g were anesthetized with halogen/oxygen and placed on a stereotaxic frame. All three animals had EEG recorded from AN and PT nuclei and transcortical sites. These animals had additional depth-electrodes placed in hippocampus. Two epidural electrodes were placed behind bregma. Depth electrodes were implanted as follows: AN-1.5-mm posterior to bregma (AP), 1.5 mm lateral to midline (L) and 6.0 mm ventral to cortical surface (D); PT-4.3-mm AP, 1.5-mm L and 6.0-mm D; hippocampus-4.5-mm AP, 4.0-mm L and 2.6-mm D. Durelon liquid glue and powder were used to hold electrodes and pedestal in place.

On the day of primary surgery, CTX screw electrodes were implanted under anesthesia. After an induction period of 2.5% halothane AN, PT and HPC twisted pair electrodes are implanted

at their respective locations. Dental cement is used to secure animals. The animals were allowed to recover for a minimal of two days. On the day of experiment, animal was placed under halothane and paralyzed with pancurouium. Blood pressure was monitored through a femoral artery and ECG was monitored. PTZ administered at a rate of 5.5 mg/kg/min after a 15min baseline EEG recording. Data was sampled at 1000Hz after being analog filtered to 300Hz.

III. RESULTS

In this section, we first demonstrate that our WTCC is a consistent method, as opposed to FFT, in measuring the common or coherent activity between two brain recordings. Having developed the WTCC method in the methodology section, we will present the results from the application of this method to cortical and subcortical field recordings.

Shown in Fig. 2. is a single epoch of the recorded field potentials from cortex, hippocampus, anterior thalamic nuclei and posterior thalamus. The recording is 16 seconds long for each channel and ictal discharges start at around 3 seconds and terminate at around 14 seconds.

A. Wavelet vs. FFT Simulation Results

A signal correlated to itself must produce the maximum autocorrelation value of 1 at all frequency bands under any analyzing windows of any length. We have compared periodogram coherence and wavelet coherence by computing the coherence of the AN signal with itself after addition of uncorrelated noise. Our results confirm that degradation of correlation value with periodogram coherence estimation is much more dramatic than WTCC under different noise amplitudes.

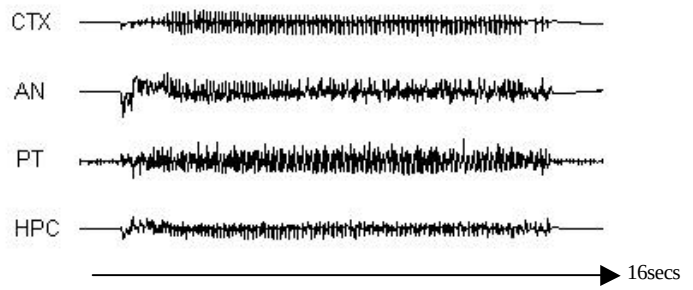

Figure 2. 4 channel EEG and depth recordings from cortex, hippocampus, anterior thalamic nuclei and posterior thalamus during the PTZ-induced seizure. Seizure starts at around 3 secs and ends at around 14 secs. Amplitudes at all channels are normalized so that each has a maximum amplitude of 1.

The simulation of time-varying coherence with addition of uncorrelated noise can be stated as below,

$$f_{AN_1} = f_{AN} + n_1$$
$$f_{AN_2} = f_{AN} + n_2 \qquad (7)$$
$$c_{f_{AN_1}, f_{AN_2}}(t) < 1 \quad if\ n_1 \neq 0\ \&\ n_2 \neq 0$$

Table 2. Wavelet auto-coherence estimation vs. FFT

SNR		∞	1	0.5	0.1
0-4Hz	Wavelets	1	0.92	0.85	0.65
	FFT	1	0.93	0.84	0.10
4-7Hz	Wavelets	1	0.99	0.96	0.68
	FFT	1	0.95	0.86	0.15
7-15Hz	Wavelets	1	0.99	0.97	0.64
	FFT	1	0.95	0.85	0.17
16-31Hz	Wavelets	1	0.93	0.82	0.43
	FFT	1	0.89	0.71	0.08
32-63Hz	Wavelets	1	0.89	0.74	0.32
	FFT	1	0.65	0.37	0.08

The results of the AN auto-coherence test under different noise power confirm that WTCC is more immune to noise than FTC. (see Table 2).

B. WTCC Results

Having confirmed the strength of WTCC over FTC in analyzing cross-coherence between EEG data, we have estimated cross-coherence across different brain centers via WTCC. The results show that there is a distinguishable coherence increase at all pairs of channels or pathways during the transition from interictal to ictal period (0.2-0.4's (data not shown) during interictal period to 0.8-0.9s during the ictal period (see table III).

In Fig. 3, we show the results from wavelet power estimation that gives us an idea about the distribution of signal power over a range of frequencies at each channel. Significant signal power is located at 16-31 frequency range for all channels.

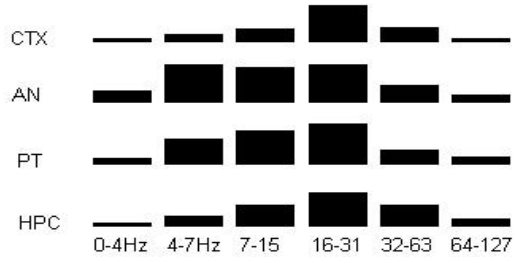

Figure 3. Power distribution of different channels over different frequency intervals during seizure ictal discharge activity. 16-31 Hz range contains the most power in all channels.

In Table 3. we show mean cross-coherence values for different range of frequencies during ictal period. Although the 16-31 Hz frequency range contains most of the power at all channels, significant cross-correlations above 0.7 exist mostly at lower frequencies, 0-7Hz. In addition, at 16-31Hz (both animals) and 7-15Hz (one animal) frequency band where primary signal powers are located, we observe a clear CTX and AN association whereas CTX-PT is being discriminated. These are only meant to be preliminary results and more animals need to be analyzed.

IV. DISCUSSION

In order to avoid problems associated with nonstationarities present in the EEG data, we preferred to use wavelets rather then the periodogram for cross-coherence estimation of two signals from different brain locations. As the

result from AN auto-coherence simulations indicate, WTCC is a better alternative for estimating the cross-coherence of two non-stationary signals. There is a distinguishable difference between

Table III: Mean ictal period cross-coherence for two animals

	PATHWAY	0-4 Hz	4-7 Hz	7-15 Hz	16-31 Hz	32-63 Hz	64-127 Hz
Animal II	AN-CTX	0.63	0.82	0.77	0.68	0.32	0.29
	AN-HPC	0.78	0.76	0.75	0.57	0.41	0.35
	AN-PT	0.63	0.73	0.51	0.51	0.33	0.32
	CTX-PT	0.76	0.87	0.49	0.53	0.44	0.31
Animal I	AN-CTX	0.69	0.71	0.56	0.60	0.45	0.35
	AN_HPC	0.66	0.60	0.58	0.53	0.37	0.33
	AN-PT	0.84	0.73	0.57	0.48	0.31	0.32
	CTX-PT	0.72	0.69	0.56	0.52	0.40	0.30

the results from WTCC and FTC where we correlated a seizure recording from AN to itself with addition of uncorrelated noise. This provides us the motivation to rely on wavelets for investigation of a possible link between two bio-signals that are nonstationary under most circumstances.

We have observed a distinguishable cross-coherence increase of varying amounts at different channels. Low (~0.3) inter-ictal cross-coherence function values reach 0.9's during ictal discharge periods in almost all channels. In addition, constructing a cross-coherence function of time has allowed us to monitor trends of cross-coherence for different pathways.

The results in Table III confirm that the recordings from AN, CTX, HPC and PT show significant level of lower-band (0-10Hz) cross-coherence in the ictal phases of the seizure activity. Although we expected to see higher cross-correlation results at the regions of the spectrum (16-31 Hz) where relatively more signal energy is concentrated, primary correlations exist at lower bands (0-10hz). High frequency bands (30Hz and higher) contained the lowest power and the lowest cross-correlation results. Furthermore, when we look at the 7-30Hz frequency range containing a significant percent of the signal powers we observe a higher CTX-AN affiliation than CTX-PT.

Furthermore, these results let us propose a distinction between local and global behavior. That is, spatially distinct brain centers are affiliated with each other solely at lower frequency bands, while higher-amplitude local behavior is uncorrelated and located at higher-frequency bands. From one perspective, we may suggest that local behavior is triggered by the global behavior or the global pacemaker signal. In other words, we may state the hypothesis that the brain locations where the recordings are made display coherent activity driven by a global signal propagating via physiologically or synaptically connected structures in the brain. A large scale coherent neural network consisting of critical centers of the brain, e.g. hippocampus, anterior thalamic nuclei and cortex, may be present further indicating that seizure propagation pathways involve components of the circuit of Papez [8].

Although we observe a significant cross-coherence increase at the ictal phase of the seizure, the maximum achieved cross-coherence values differ at each pathway. While at some pathways, e.g., CTX-AN, coherence values reach above .9 (data not shown), at some other pathways, e.g. AN-PT, HPC-PT, the cross-coherence values fluctuate at lower values. While the cross-coherence values are significant, the relative magnitude of them may provide us insight about the functional distance between two brain locations. In other words, the coherence value may be an indicator of a direct or indirect link between two brain centers whose epileptic activity is analyzed. Finally, although the data is not shown, cross-correlation estimation functions (3) maximize at non-zero delay values supporting the existence of propagation phenomenon.

The behavior observed in the EEG recordings analyzed in this paper lets us make the proposition that the primary epileptogenic zone of unknown location acts as a global discharge initiator. We are also able to make the assumption that the generated discharge signal is carried to cortical and subcortical brain centers via synaptic connections where it produces quasi-periodic activity of diverse signal morphology depending on the type and the physiological state of the underlying neural tissue.

III.CONCLUSION

We have shown that the cross-coherence estimation method derived from wavelet transform can help us identify brain elements that are coherently involved in the seizure activity. The level of coherence obtained is suggested to be a potential indicator of functional distance between two brain centers, e.g. PT is less affiliated to CTX than AN. Finally, we showed significant ictal period cross-coherence values achieved using WTCC as a potent method for non-stationary bio-signal analysis.

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