Gamma (30-80Hz) Bicoherence Distinguishes Seizures in the Human Epileptic Brain

Marija Cotic-*EMBS Student Member*, Yotin Chinvarun, Mirna Guirgis-*EMBS Student Member*, Peter L. Carlen, and Berj L. Bardakjian, *IEEE Member*

***Abstract*— We have applied wavelet bicoherence (BIC) analysis to human iEEG data to characterize non-linear frequency interactions in the human epileptic brain. Bicoherence changes were most prominent in the gamma (30-80 Hz) frequency band, and allowed for the differentiation between seizure and non-seizure states in all patients studied (n=3). While gamma band BIC values increased during seizure activity, this trend was only observed in a select number of electrode(s) located on the implanted patient subdural grids. Several studies have suggested that fast frequencies may play a role in the process of seizure genesis. While the small patient numbers limit the significance of our study, our results highlight the bicoherence of the gamma frequency band (30-80 Hz) as an ictal identifier, and suggest an active role of this fast frequency during seizures.**

I. Introduction

A large area of brain research is focused on the study of neuronal oscillations, their associations and interactions, as brain rhythms are believed to play a large role in establishing communication between regions during regular or pathological brain states [1, 2]. In the abnormal brain, neuronal oscillations have been identified as a key mechanism in epilepsy, where pathological entrainment is a prominent characteristic of seizure activity [3].

Many linear and non-linear estimators have been developed to study functional couplings in areas of the brain during regular tasks or comprised activity. Such interactions may be investigated by examining frequency interactions between neuronal recordings. The bicoherence estimator provides a measure of non-linear interactions in a single signal or between two signals.

Here, we have applied wavelet bicoherence analysis to study neuronal phase couplings in intracranial electroencephalograph (iEEG) recordings, encompassing seizure and non-seizure activity from three patients with extratemporal lobe epilepsy (ETLE).

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Marija Cotic is with the Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, ON, Canada (corresponding author; e-mail: marija.cotic@utoronto.ca).

Yotin Chinvarun is with the Comprehensive Epilepsy Program, Phramongkutklao Hospital, Bangkok, Thailand.

Mirna Guirgis is with the Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, ON, Canada

Peter L. Carlen is with the Toronto Western Research Institute, Toronto, ON, Canada.

Berj L. Bardakjian is with the Edward S. Rogers Sr. Department of Electrical and Computer Engineering and the Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, ON, Canada.

II. Patient Selection and Data Acquisition

Patient studies were conducted by the Thailand Comprehensive Epilepsy Program, at the Phramongkutklao Hospital (Bangkok, Thailand). Intracranial EEG data were collected from three patients with ETLE, undergoing pre-surgical evaluation for epilepsy surgery. All patients underwent surgery for the placement of intracranial grids, arranged in a 64 contact (8x8) grid pattern (PMT, Chanhassen, MN, U.S.A.). Recordings were sampled at 2000 Hz (Stellate, Montreal, QC, Canada) and referenced to electrodes located behind the ears (linked ears), but subsequently arranged offline in a bipolar arrangement in order to diminish artifacts. Electrical noise, 50 Hz and harmonics, were removed using FIR notch filtering. All analyses were performed using MATLAB (The MathWorks, Natick, MA, U.S.A.).

The recorded iEEG data were independently reviewed off-line by a neurologist. Seizure start and end times were defined electrographically via the electrode(s) with the earliest seizure activity.

III. Algorithms

Wavelet BIC analysis was used to study a seizure episode from each patient. The iEEG data segments analyzed were comprised of a single seizure, as well as (on average) more than one minute of iEEG activity leading up to and following the seizure, to allow for the study of both non-seizure and seizure activity. Auto BIC, which uses the frequency components in one channel, was measured for all electrodes on the implanted patient grids for the data segments described above.

Bicoherence measures the relationship between underlying oscillatory components of an observed signal. More specifically, it examines the relation between every possible pair of frequency components, f_1 and f_2, (which ranged from 1 to 149 Hz in this study) in a signal and their sum ($f_3 = f_1 + f_2$).

The bispectrum and bicoherence can be estimated using the wavelet transform. The wavelet based bispectrum is defined as [4]:

$$B^W_{xyx}(\sigma_1,\sigma_2,T) = \int_T W_x(\sigma_1,\tau) W_y(\sigma_2,\tau) W^*_x(\sigma,\tau)\, d\tau \qquad (1)$$

where σ_1 and σ_2 correspond to scales of the wavelet

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transform and $\frac{1}{\sigma}=\frac{1}{\sigma_1}+\frac{1}{\sigma_2}$, which is equivalent to $f=f_1+f_2$ for an interval *T*. The wavelet-based bicoherence follows as:

$$b_{xyx}^{W}(\sigma_1,\sigma_2,T)=\frac{\left|B_{xyx}^{W}(\sigma_1,\sigma_2,T)\right|}{\sqrt{\int_T\left|W_x(\sigma_1,\tau)W_y(\sigma_2,\tau)\right|^2 d\tau\int_T\left|W_x^*(\sigma,\tau)\right|^2 d\tau}} \quad (2)$$

Wavelet bicoherence ranges from 0 to 1, with a value of zero representing no coupling between two signals.

We calculated the wavelet BIC, using the complex Morlet wavelet, for frequency scales f_m, where f_m ranged from 1 to 149 Hz, in steps of 4 Hz, and for sliding time windows of 1-second duration. A non-seizure (T = 50-51 seconds) BIC matrix profile and seizure (T = 126-127 seconds) BIC matrix profile are illustrated in fig. 1 (for patient one). Mean BIC values were calculated along the anti-diagonal (fig. 1) to obtain estimates of BIC for various frequencies f_3 . Global BIC values were then calculated from mean BIC values to obtain estimates of cross-frequency coupling within the analyzed frequency range of (1-149) Hz, during non-seizure and seizure activity.

IV. Results

Wavelet BIC profiles were calculated for non-seizure and seizure iEEG segments for all electrodes on the implanted grids. While BIC profiles varied in space and time, and across patients, increased BIC values were visually observed during seizures (fig. 1). Electrodes possessing high BIC values were further explored, to elucidate the frequency spread of neuronal phase interactions.

Mean BIC values, calculated across the anti-diagonal, are depicted in fig. 2 for one channel from each patient. The iEEG recording for each channel is shown at top, with the seizures marked by a horizontal line. Seizure times were assessed off-line by a neurologist. Mean BIC values are shown for various frequencies f_3, ranging from (5-9) Hz at the lowest and (77-81) Hz at the highest. In patients 1 and 3, the seizure is visible for BIC values of various frequency ranges, corresponding to f_3, while mean BIC values are high prior to and during the seizure, and drop off at the end of the seizure in patient 2. For all three patients, mean BIC values were observed to maximally increase in frequencies $f_3 <$ 80Hz.

Next, the eigenvalue spectrums (λ_i) for all BIC matrices were computed for all time windows. The eigenization was limited to the (1-81) Hz frequency range (ie. $f_1 = f_2 =$ 1:4:81), where the maximal mean BIC was observed. The resulting distribution of eigenvalues is related to the bicoherence of the signal, with the amplitude proportional to the amount of frequency interaction estimated via BIC. The maximum eigenvalue, $\lambda_{\max}$, is plotted across time in fig. 2C. Similar to the mean BIC values, $\lambda_{\max}$, was able to distinguish the non-seizure and seizure states, using BIC values in the (1-81) Hz frequency range.

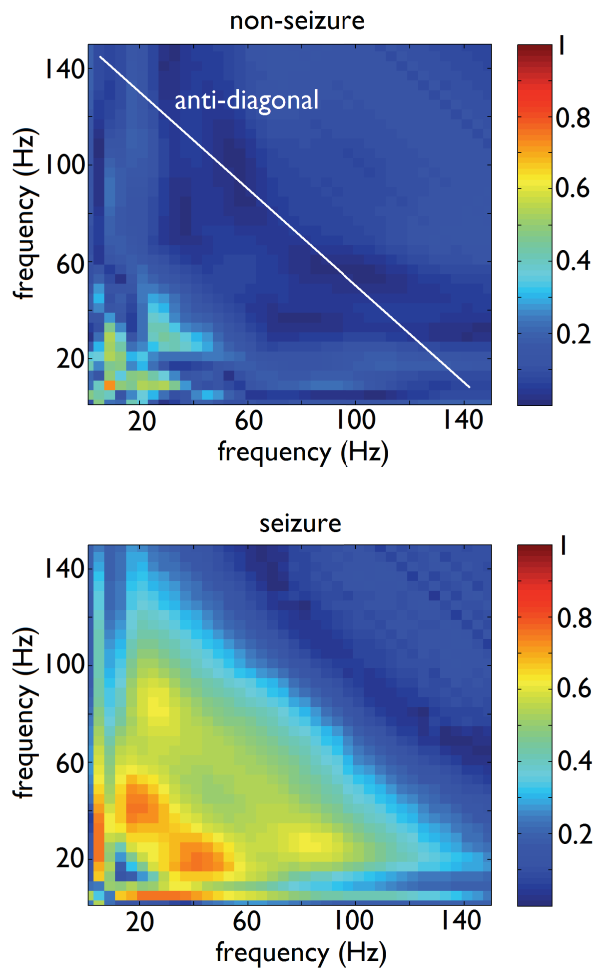

Figure 1. An example of a non-seizure (T=50-51 seconds) bicoherence matrix (top) and seizure (T=126-127 seconds) bicoherence matrix (bottom) for patient 1.

Global BIC values were then calculated for seizure and non-seizure states. The ratio of seizure to non-seizure global BIC values for the (1-149) Hz frequency range are shown in fig. 3. Maximal BIC increases were observed in the (30-80) Hz frequency range.

V. Discussion

In a previous study, examining the auto-bicoherence of iEEG in sleep, wakefulness and seizures, it was reported that bicoherence was typically low or not generally present during the awake state, while BIC was elevated during sleep and seizures, when compared to the awake state [5]. Here, we have similarly demonstrated the ability of BIC values to distinguish the non-seizure and seizure states. More specifically, our results demonstrate that gamma band activity (30-80 Hz) was observed to attain the highest seizure BIC values, relative to the non-seizure state.

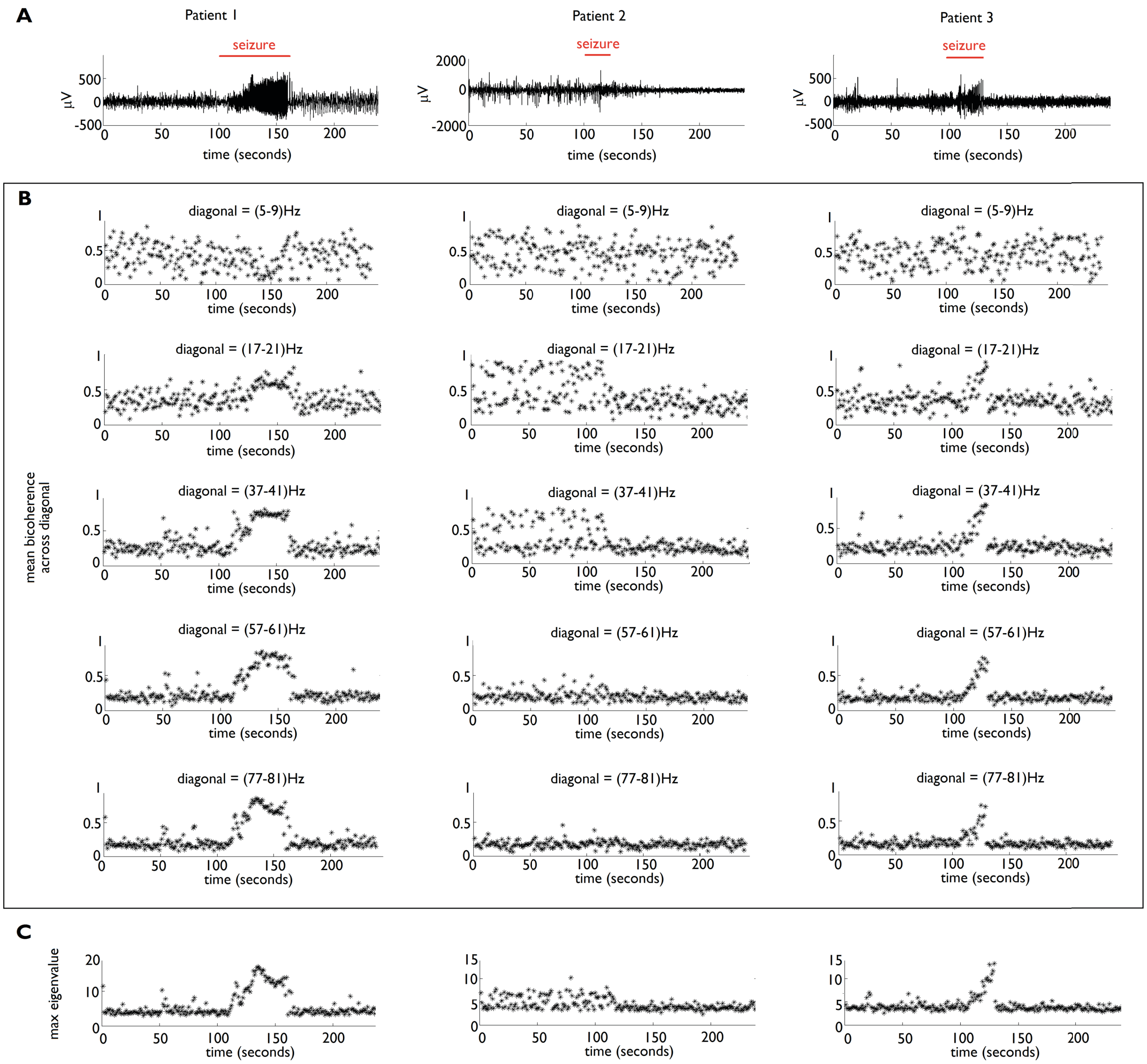

Figure 2. A: Intracranial EEG traces for three patients. The seizure is marked by the horizontal line. **B:** Mean bicoherence values calculated from the diagonal of bicoherence matrices, of 1-second sliding windows in time and for the indicated frequency ranges. **C:** The maximum eigenvalue plotted in time, where the max eigenvalue was computed from the eigenization of (1-80) Hz by (1-80) Hz bicoherence matrices (calculated for 1-second windows over time.

Gamma activity (30-100 Hz) has been proposed to play a role in connecting spatially distributed brain activities [6]. Similarly, the gamma frequency is a prominent coherent oscillation observed in the healthy hippocampi of humans and rodents [7]. Furthermore, several studies have suggested a prominent interaction with slower frequencies (i.e. gamma-theta coupling) [8].

Gamma activity dysfunction has also been associated with the epileptic state. The spectral presence of the (30-80 Hz) frequency band has been observed in epileptiform discharges and it has been reported that pro-convulsant drugs help induce gamma oscillations [7].

While gamma band BIC values increased during seizure activity, this trend was spatially dependent, as these increases were only observed in a select number of electrode(s) located on the implanted patient subdural grids. The low number of electrodes displaying elevated BIC values during seizures, compared to the non-seizure state, is perhaps suggestive of a pathological zone in the cortex. Future studies relating these identified areas to seizure onset zones may yield additional insights regarding this rhythm.

The small patient numbers limit the significance of our study. However, we believe this study highlights the bicoherence of the gamma frequency band (30-80 Hz) as an ictal identifier, and suggests an active role of this fast frequency during seizures.

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