31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Regression-based analysis of synchronization in multichannel EEG in epilepsy

Andreas Graef, Manfred Hartmann, Manfred Deistler and Tilmann Kluge

Abstract— **In this paper we assess a dependency measure for multivariate time series termed Extrinsic-to-Intrinsic-Power-Ratio (EIPR) using two different signal models. In a comparison with Partial Directed Coherence (PDC) we show that both measures correctly identify imposed couplings, but that limitations of the PDC do not affect EIPR. Moreover, EIPR is successfully used for the localization of the seizure onset zone in ECoG recordings from two epilepsy patients, given the exact seizure onset time. The electrodes identified by the proposed method are in excellent accordance with the clinical findings.**

I. Introduction

A. Background

Epileptic seizures reflect an excessive and hypersynchronous activity of neurons in the brain. They originate from a certain region in the brain and may spread out over other areas. Localization of the seizure onset zone is an important task for the clinical therapy, in particular in the course of pre-surgical clarification. In order to identify the focus of the epileptic zone, the manual visual inspection of raw invasive EEG (i.e. ECoG, *electrocorticogram*) data is currently still state of the art. Therefore an improvement of the analysis of seizure initiation using mathematical models is clinically desired: Identifying the spatio-temporal dependencies in ictal ECoG recordings could fulfill this task.

A common approach to the analysis of coupling effects in neural signals is autoregressive modeling. Numerous measures based on this linear framework have been published [1]. We mention two directed ones which are based on a spectral analysis of the autoregressive model: the *Directed Transfer Function (DTF)* [2] and the *Partial Directed Coherence (PDC)* [3]. The later is closely linked to Granger causality, a widely-used concept of dependency in multivariate time series [4].

Both measures have often been applied to neural signals for epileptic seizure analysis [5], [6], [7], [8]. Only recently Wilke et al. [9] proposed a time-variant version of the DTF for epileptic seizure onset zone detection, which shows promising first results.

Hartmann et al. [10] suggested another approach to the measurement of dependencies: Instead of performing a spectral analysis within the autoregressive framework, the direct evaluation of regression terms reveals coupling effects. They are the basis for a dependency measure termed *Extrinsic-to-Intrinsic-Power-Ratio (EIPR)*.

B. Contributions

In this paper we assess the properties of the EIPR by comparing it to the widely used PDC. We test the ability of the EIPR to correctly indicate dependencies imposed by signal models. Moreover, with the help of simulations and theoretical reflections we show that our measure is not affected by limitations which apply to the PDC in certain situations.

Furthermore we apply the EIPR to epileptic ECoG data in order to localize the seizure onset zone of patients suffering from temporal lobe epilepsy. The identification of this area is based on the analysis of the EIPR calculated in the given initial seconds of the seizure, revealing coupling effects between electrodes during this early propagation stage.

II. Method

The analysis of multi-channel ECoG data uses real-valued multivariate signals, which consist of K *channels* $x_k[n]$, $k = 1, ..., K$ ($n \in \mathbb{Z}$ denoting the time index). These signals are assumed to be zero-mean and short-term stationary, i.e. the statistics do not depend on the time index n within a sufficiently short time window of sample length N_{win}.

A. Autoregressive model

The DTF and the PDC analyze spectral properties of the AR model. In contrast, in [10] we proposed to identify synchronizations by regarding regression terms as described below. We refer to [10] for a detailed discussion of our approach and only recall the basic idea here:

For the purpose of measuring couplings, we define the *partial contribution* $x_{k,l}[n]$ as

$$x_{k,l}[n] \triangleq \sum_{s=1}^{p} A_{k,l}[s]\, x_l[n-s]. \tag{1}$$

This allows to write an autoregressive model of order p in decomposed form for each channel $x_k[n]$, $k = 1...K$ as

$$x_k[n] = \sum_{l} x_{k,l}[n] + \epsilon_k[n], \tag{2}$$

where $\epsilon_k[n]$ is white noise. The model coefficients $A_{k,l}[s]$ have to be estimated from the data.

Thus each $x_{k,l}[n]$ in (2) reflects the contribution from the respective channel x_l onto channel x_k. For $l \neq k$, we speak about the *partial extrinsic contribution*, for $l = k$ about the *intrinsic contribution*.

Manuscript received April 23, 2009

A. Graef (e-mail: andreas.graef@ait.ac.at), M. Hartmann and T. Kluge are with AIT Austrian Institute of Technology GmbH, Safety and Security Department; Vienna, Austria

M. Deistler is with Vienna University of Technology, Institute for Mathematical Methods in Economics; Vienna, Austria

B. Extrinsic-to-Intrinsic-Power-Ratio (EIPR)

We expect mutual dependencies of the multivariate signal $x_k[n]$ to indicate synchronization and coupling effects of brain regions during epileptic seizures. In [10] we therefore proposed to consider measures based on the variance of $x_{k,l}[n]$ in (2). In order to render them scale-independent, a normalization is needed assuring that the measure takes large values in case of increased inflow from channel x_l onto x_k, independently of the signal power.

In [10] it was suggested to normalize the variance term $\mathbb{V}\{x_{k,l}[n]\}$ by defining the ratio

$$\eta^2_{k,l} \triangleq \frac{\mathbb{V}\{x_{k,l}[n]\}}{\mathbb{V}\{x_{k,k}[n]\}}, \tag{3}$$

termed *Extrinsic-to-Intrinsic-Power-Ratio (EIPR)*. It quantifies coupling or synchronization effects of channel pairs (x_l, x_k), taking large values for large partial extrinsic and small intrinsic power.

C. Partial Directed Coherence (PDC)

In Subsection I-A we mentioned that a common approach of investigating couplings is to regard measures based on a spectral analysis of the multivariate AR model. Among them, we consider the PDC [3] due to its mathematical properties such as its link to Granger causality. We will compare it to the EIPR in this paper.

The PDC is based on the Fourier-transformed AR model coefficients and normalized with respect to all target channels:

$$\pi^2_{k,l}(f) \triangleq \frac{|A_{k,l}(f)|^2}{\sum_{n=1}^{K} |A_{n,l}(f)|^2}. \tag{4}$$

Here, $A_{k,l}(f) = \delta_{k,l} - \mathfrak{F}_{s\to f}\, A_{k,l}[s]$, where $\delta_{k,l}$ denotes the Kronecker delta and $\mathfrak{F}_{s\to f}$ the Fourier transformation.

The PDC is bounded by 0 and 1. If $\pi^2_{k,l}(f) \equiv 0\, \forall f$, one can conclude that there is no direct dependency from x_l onto x_k. As it is unlikely in applications that one observes values of the PDC exactly matching zero, one has to statistically test whether values of the PDC are significantly different from zero. Thus Schelter et al. [11] derived an asymptotic frequency-dependent confidence interval: For each frequency f, PDC values below the respective threshold indicate the absence of any direct coupling.

D. Signal models

In order to assess the capability of the EIPR to correctly detect coupling effects in multivariate signals, we test it on simulated AR signals.

For facilitating comparison with measures in literature, we choose a multivariate autoregressive system of order $p = 5$ as proposed in [1]:

$$\begin{cases} x_1[n] = 0.8\, x_1[n-1] + 0.65\, x_2[t-4] + \epsilon_1[n] \\ x_2[n] = 0.6\, x_2[n-1] + 0.6\, x_4[n-5] + \epsilon_2[n] \\ x_3[n] = 0.5\, x_3[n-3] - 0.6\, x_1[n-1] + \ldots \\ \qquad\quad \ldots + 0.4\, x_2[n-4] + \epsilon_3[n] \\ x_4[n] = 1.2\, x_4[n-1] - 0.7\, x_4[n-2] + \epsilon_4[n] \end{cases} \tag{5}$$

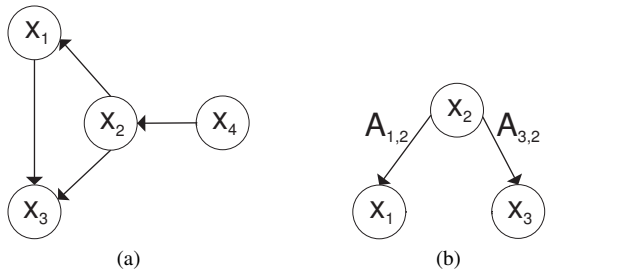


Fig. 1. Dependency paths of AR signal models. Graph (a) illustrates model (5), graph (b) model (6).

The dependency paths of this model are shown in Fig. 1 (a).

In order to test the influence of different target channels, we simplify the dependency structure of model (5) and consider the following AR model of order $p = 1$:

$$\begin{cases} x_1[n] = 0.8\, x_1[n-1] + 0.65\, x_2[n-1] + \epsilon_1[n] \\ x_2[n] = 0.6\, x_2[n-1] + \epsilon_2[n] \\ x_3[n] = 0.5\, x_3[n-1] + A_{3,2}\, x_2[n-1] + \epsilon_3[n] \end{cases} \tag{6}$$

This model will be simulated with different values of $A_{3,2}$ in Subsection II-D, revealing the difference in the behavior of the PDC and the EIPR. The imposed dependencies together with the respective AR model coefficients are illustrated in Fig. 1 (b), which is a subgraph of the initial system in Fig. 1 (a).

E. ECoG data acquisition

In Subsection III-B the EIPR is applied to neural signals for the determination of the epileptic seizure onset zone. The ECoG data used in this study consist of 28 channels and are taken from two patients in Vienna General Hospital, Department of Neurology, "Patient A" and "Patient B". Both patients were suffering from medical refractory temporal lobe epilepsy. The ECoG signals were obtained in the course of a presurgical examination, each lasting for approximately one week, and referenced to an electrode outside of the seizure focus. After recording, line interference was removed using a notch filter at 50 Hz, and the signals were low-pass filtered at 64 Hz in order to avoid aliasing and downsampled from 256 Hz to 128 Hz sampling rate.

III. Results

A. Assessment of EIPR and PDC

In order to test the performance of the EIPR, we first apply it to the signal model (5) whose dependencies are well detected by the PDC [1]. As Table I details, our measure correctly identifies the imposed dependencies: The columns of the table indicate the source channels, the rows the targets: Thus, the (k,l)-element quantifies the influence from x_l onto x_k. Dependencies, which are imposed by (5), are set in bold-face type. They are considerably higher than the others, thus properly reflecting the structure of the AR model (5) symbolized in Fig. 1 (a).

In order to further investigate coupling effects, we simulate model (6), whose imposed dependencies are illustrated in

TABLE I

VALUES OF THE EIPR FOR SIGNAL MODEL (5). IMPOSED DEPENDENCIES (BOLD VALUES) ARE CORRECTLY RECOGNIZED.

$\eta^2_{k,l}$	x_1	x_2	x_3	x_4
x_1	1.0000	**0.1730**	0.0004	0.0001
x_2	0.0013	1.0000	0.0011	**0.7238**
x_3	**1.9094**	**0.2498**	1.0000	0.0002
x_4	0.0012	0.0007	0.0012	1.0000

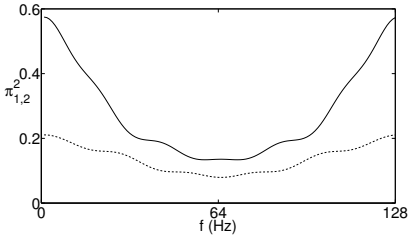


Fig. 2. PDC plots for model (6). PDC $\pi^2_{1,2}$ for $A_{3,2} = 1.2$ (dashed line) is damped compared to the initial plot for $A_{3,2} = 0.4$ (solid line), whereas EIPR is not affected by this modification by definition.

Fig. 1 (b), twice with different parameters $A_{3,2} = 0.4$ and $A_{3,2} = 1.2$. Assume that we are interested in the coupling between channels x_2 and x_1, channel x_3 given but not considered. The alteration of the parameter $A_{3,2}$ changes the coupling (x_2, x_3) which we are not interested in. We thus demand that this modification of the system must not affect our observed dependency, say (x_2, x_1).

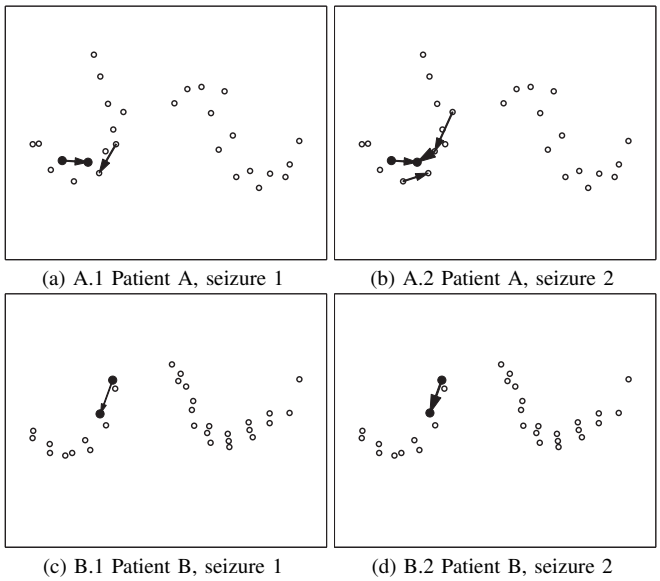
When applying the EIPR to the two simulated versions of model (6) respectively, the imposed dependencies are correctly recognized, and we obtain the same value of $\eta^2_{2,1}$ in both simulations. The situation for the PDC is different: Fig. 2 shows plots of the PDC $\pi^2_{2,1}(f)$ for $A_{3,2} = 0.4$ (solid line) as well as for $A_{3,2} = 1.2$ (dashed line). Although the PDC values are significantly different from zero according to the confidence interval in either case and thus correctly indicate the imposed coupling, they are affected by the third channel. The PDC resulting from the parameter modification is damped compared to the initial one – a behavior we wanted to avoid.

B. Application to neural data

We apply the EIPR and the PDC to ECoG recordings from epilepsy patients for the analysis of the seizure onset zone. Its identification is based on the analysis of the EIPR calculated in the initial seconds of the seizure, given the onset time.

The ECoG data used for this purpose were acquired as described in Subsection II-E, representing a total of four seizures. For each seizure, the statistics were calculated within a window of 4 seconds covering the beginning of the respective seizure. Thus, our measure indicates coupling effects between electrodes during this early propagation stage of the seizure.

The estimated statistics were used for the identification of four AR models, each of order $p = 7$. In order to increase numerical stability of the AR model identification, a channel selection algorithm was used which is described in detail in [10]: Its basic idea is that for the regression of each channel x_k, a limited number of channels x_l is chosen in (2).



(a) A.1 Patient A, seizure 1 (b) A.2 Patient A, seizure 2

(c) B.1 Patient B, seizure 1 (d) B.2 Patient B, seizure 2

Fig. 3. Detection of the seizure onset zone. (a) and (b) show the onset zone of two seizures A.1 and A.2 of patient A, (c) and (d) the ones of the two seizures B.1 and B.2 of patient B. Arrows indicate the EIPR, electrodes identified by clinicians are represented by filled circles. In all cases, our results coincide well with the clinical description.

The results obtained are illustrated in Fig. 3. The upper line shows two seizures of patient A, the line at the bottom two of patient B. In each of the four graphs, the circles represent the spatial layout of the electrodes, and the arrows indicate values of EIPR between two electrodes. Hereby, $\eta^2_{k,l}$ is symbolized by an arrow from electrode x_l to x_k. Values below a manually set threshold were suppressed in order to obtain clear pictures. Different thresholds were chosen for each seizure such that only a few dominant arrows remain. Electrodes which belong to the seizure onset zone according to the findings of clinicians, who visually inspected the raw ECoG recordings, are symbolized by filled circles. The involved electrodes therefore represent the seizure onset zone as indicated by the proposed method.

In contrast to the results in Fig. 3 obtained by application of the EIPR, the use of the PDC with the described ECoG data did not yield any exploitable findings (results not shown).

IV. DISCUSSION

A. Comparison of EIPR and PDC

In Subsection II-D we showed that the EIPR correctly identifies dependencies in model situations. In contrast to the PDC, the EIPR is not influenced by neighborhood channels not being considered.

For an explanation consider the denominator of the PDC: When we study the coupling between two specific channels, the measure indicating their dependency is influenced by additional channels we are not directly interested in (cf. [12]). This is easy to see when considering the model (6) depicted by Fig. 1 (b): Changing the value of the AR model coefficient

$A_{3,2}$ (which we do *not* consider) affects the denominator of the PDC $\pi^2_{1,2}(f)$ which is given by

$$\pi^2_{1,2}(f) = \frac{|A_{1,2}(f)|^2}{|A_{1,2}(f)|^2 + |A_{2,2}(f)|^2 + |A_{3,2}(f)|^2} .$$

The PDC plots in Fig. 2 reflect this fact. Contrarily, following our approach, the EIPR is not concerned by this problem. This follows directly from the definition of the partial contributions (1) the EIPR is based on.

One could claim that this limitation is only caused by the fact that the PDC is normalized with respect to all target channels. However, normalizing with respect to all source channels as proposed in [12] causes similar limitations.

This means that in the case of ECoG signals our observation of brain activity between two examined electrodes indicated by the PDC would be influenced by the measurements of other electrodes. This is a perturbing limitation, as the signals recorded by these complementary electrodes compromise our observation. Assume, for example, a seizure focus located in the middle below three electrodes. The signals recorded depend of course on their exact position on the cortex. When studying the brain activity between two of them, our result is influenced by the position of the third electrode, which we cannot adapt to our needs. These reflections motivate our approach using the EIPR.

In order to underline the appropriateness of the EIPR we finally note that measures such as the PDC or the DTF, which are based on a spectral analysis, are frequency dependent. Condensing them for graphical representation, e.g. by integrating over specific frequency bands, poses problems: Apart from the fact that we lose potentially important information, it is not obvious at all how to interpret integrated coherences, as the obtained value does not reflect any physical property. Furthermore, these frequency bands would have to be chosen explicitly, what we want to avoid for practical reasons. Contrarily, the EIPR $\eta^2_{k,l}$ measuring the coupling between two channels x_l and x_k is a scalar, allowing an intuitive representation in two-dimensional graphs (such as Fig. 1).

B. Seizure onset zone detection

As Fig. 3 illustrates, the application of the EIPR to ECoG recordings from epilepsy patients for seizure onset zone detection yields promising first results. In all four cases shown we were able to identify the electrodes which were specified by the clinicians in their findings after visual inspection of the raw signals.

Interestingly, regarding both seizures A.1 and A.2 of Patient A (depicted in the upper row), our measure also indicates electrodes which were – according to the clinical findings – only involved some seconds later due to seizure propagation. In the case of seizure A.1, their involvement started about one second later. In the case of seizure A.2, however, we observe an anticipation of five seconds, which is outside the employed window of four seconds. Thus the question arises whether the EIPR might be able to identify latent statistical changes of the signal which are not easily visible in the raw ECoG signal at that moment.

Considering Patient B, whose two seizures B.1 and B.2 are shown in the row at the bottom of the figure, our results exactly match the clinical findings claiming two electrodes initially involved.

V. Conclusion

In this paper we compared the EIPR to the PDC with the help of signal models. We showed that the EIPR has, in contrast to the PDC, the properties we demand for a dependency measure appropriate for analyzing the couplings in multivariate neural signals. Moreover, the application of the EIPR to epileptic ECoG data for the detection of the seizure onset zone yields promising first results.

Our method could therefore have the potential to assist clinicians with their diagnosis and thereby help to localize the seizure onset zone. However, this requires further research in order to investigate properties of the EIPR in more detail and to apply it to a larger data basis.

Acknowledgments

The authors would like to thank Prof. Baumgartner for providing the ECoG data.

References

[1] M. Winterhalder, B. Schelter, W. Hesse, K. Schwab, L. Leistritz, D. Klan, R. Bauer, J. Timmer, and H. Witte, "Comparison of linear signal processing techniques to infer directed interactions in multivariate neural systems," *Signal Processing*, vol. 85, pp. 2137–2160, 2005.

[2] M. Kaminski and K. Blinowska, "A new method of the description of the information flow in the brain structures," *Biological Cybernetics*, vol. 65, pp. 203–210, 1991.

[3] L. Baccala and K. Sameshima, "Partial directed coherence: a new concept in neural structure determinations," *Biological Cybernetics*, vol. 84, pp. 463–474, 2001.

[4] C. Granger, "Investigating causal relations by econometric models and cross-spectral methods," *Econometrica*, vol. 37, pp. 424–438, 1969.

[5] P. Franaszczuk and G. Bergery, "Application of the Directed Transfer Function Method to Mesial and Lateral Onset Temporal Lobe Seizures," *Brain Topography*, vol. 11, no. 1, pp. 13–21, 1998.

[6] M. Ge, X. Jiang, Q. Bai, S. Yang, J. Gusphyl, and W. Yan, "Application of the Directed Transfer Function Method to the Study of the Propagation of Epilepsy Neural Information," *IEEE EMBS Proceedings Lyon 2007*, pp. 3266–3269, 2007.

[7] K. Sameshima and L. Baccala, "Using partial directed coherence to describe neuronal ensemble interactions," *Journal of Neuroscience Methods*, vol. 94, pp. 93–103, 1999.

[8] L. Astolfi, F. Cincotti, D. Mattia, M. Lai, L. Baccala, F. de Vico Fallani, S. Salinari, M. Ursino, M. Zavaglia, and F. Babiloni, "Comparison of different multivariate methods for the estimation of cortical connectivity: simulations and applications to EEG data," *IEEE EMBS Proceedings Shangai 2005*, pp. 4484–4487, 2005.

[9] C. Wilke, L. Ding, and B. He, "Estimation of Time-Varying Connectivity Patterns Through the Use of an Adaptive Directed Transfer Function," *IEEE Transactions on Biomedical Engineering*, vol. 55, no. 11, pp. 2557–2564, 2008.

[10] M. Hartmann, A. Graef, H. Perko, C. Baumgartner, and T. Kluge, "A Novel Method for the Characterization of Synchronization and Coupling in Multichannel EEG and ECoG," *WASET Proceedings Venice 2008*, vol. 34, pp. 6–11, 2008.

[11] B. Schelter, M. Winterhalder, M. Eichler, M. Peifer, B. Hellwig, B. Guschlbauer, C. Lücking, R. Dahlhaus, and J. Timmer, "Testing for directed influences among neural signals using partial directed coherence," *Journal of Neuroscience Methods*, vol. 152, pp. 210–219, 2005.

[12] B. Schelter, J. Timmer, and M. Eichler, "Assessing the strength of directed influences among neural signals using renormalized partial directed coherence," *Journal of Neuroscience Methods*, 2009.