Quantitative Analysis of Peri-Ictal Multi-Channel EEG*

Christian Rummel1, Ralph G. Andrzejak2 and Kaspar Schindler3
1 Support Center for Advanced Neuroimaging, Institute for Diagnostic and Interventional Neuroradiology, Inselspital, Berne
2 Department of Information and Communication Technologies, Universitat Pompeu Fabra, Barcelona, Spain
3 Department of Neurology, Inselspital, Berne

Summary

Visual analysis of EEG signals by clinical experts remains the “gold standard”, but is increasingly complemented by quantitative methods, which offer more objective criteria for assessment and may indicate subtle signal changes possibly escaping even the trained observer’s eye. With regard to the EEG of epilepsy patients two key applications of quantitative EEG (qEEG) analysis methods are early detection or even prediction of seizures and the localization of ictogenic tissue.

qEEG methods can be categorized by the number of signals that are investigated as potentially interacting units (univariate, bivariate, multivariate). In addition, methods can be distinguished by the character of signals or interaction properties (linear or nonlinear). Finally, it can be investigated, whether EEG signals are in a causal relation, thus driving or being driven by others.

In the present article, examples of different qEEG methods as used at the epilepsy unit of the University of Berne are demonstrated by analysing peri-ictal, intracranial EEG. We discuss possible clinical implications and limitations of qEEG methods as well as perspectives for future developments.

Epileptologie 2012; 29: 99 – 113

Key words: quantitative EEG analysis, epilepsy surgery, networks

Quantitative Analyse peri-iktaler Vielkanal-EEG-Daten

Die visuelle Analyse von EEG-Signalen durch klinische Experten wird zunehmend erweitert durch die Verwendung quantitativer Methoden. Letztere sollen einerseits objektivere Kriterien bieten und andererseits auch subtile Veränderungen von Signaleigenschaften anzeigen, die selbst dem geschulten Auge möglicherweise entgehen. Im Hinblick auf das EEG von Epilepsie-

patienten bestehen die Hauptanwendungen quantitativer EEG (qEEG) Analysemethoden in der frühen Erkennung oder gar Vorhersage von epileptischen Anfällen sowie in der Lokalisation von iktogenem Gewebe.

qEEG-Methoden können nach der Anzahl der Signale kategorisiert werden, die als möglicherweise wechselwirkende Untereinheiten untersucht werden (uni-, bi- oder multivariat). Weiter kann nach dem Charakter der Signal- oder Wechselwirkungseigenschaften unterschieden werden (linear oder nichtlinear). Schliesslich kann untersucht werden, ob EEG-Signale miteinander in einer kausalen Beziehung stehen, also andere treiben oder von diesen getrieben werden.

Im vorliegenden Artikel werden anhand von periiktalem, intrakraniellem EEG Beispiele für verschiedene an der Abteilung für Epileptologie der Universität Bern angewendete Varianten der qEEG-Analyse demonstriert. Es wird diskutiert, welche klinischen Rückschlüsse sich aus den Resultaten ziehen lassen. Limitationen sowie Entwicklungsperspektiven quantitativer Analysemethoden werden aufgezeigt.

Schlüsselwörter: quantitative EEG Analyse, Epilepsie-

chirurgie, Netzwerke

*Acknowledgements
CR and KS received support by Schweizerischer Nationalfonds (project nos. 320030-122010 and 33CM30-124089). RGA acknowledges grant FIS-2010-18204 of the Spanish Ministry of Education and Science.

Copyright
The copyright for all figures remains with the authors.
Analyse quantitative des données péri-ictales de quatre canaux EEG

Les méthodes quantitatives viennent de plus en plus s’associer à l’analyse visuelle de signaux EEG par les experts cliniques. Leur but est de fournir des critères plus objectifs et aussi de mettre en évidence des modifications subtiles dans les caractéristiques des signaux qui peuvent échapper même à l’œil le plus expérimenté. En rapport avec l’EEG de patients épileptiques, les principales applications de méthodes d’analyse quantitative de l’EEG (qEEG) consistent à dépister précoce et même anticiper des crises épileptiques, ainsi qu’à localiser le tissu ictogène.

Les méthodes qEEG peuvent être classées en fonction du nombre de signaux qui sont étudiés comme sous-entités potentiellement interactives (uni-, bi- ou multivariées). On peut également faire une distinction en fonction du caractère des propriétés du signal ou des effets interactifs. Enfin, on peut examiner une éventuelle relation causale entre les signaux de l’EEG, en d’autres termes, voir s’ils génèrent d’autres signaux ou sont eux-mêmes générés par d’autres signaux.

Dans le présent article sont démontrées à l’appui de l’EEG péri-ictal intracrânien différentes variantes d’analyses qEEG appliquées au département d’épileptologie de l’Université de Berne. Les conclusions cliniques qui peuvent être tirées des résultats sont discutées et l’article met aussi en lumière les limites de même que les perspectives de développement des méthodes d’analyse quantitative.

Mots clés : analyse quantitative de l’EEG, chirurgie épileptique, réseaux

Introduction

Épilepsie est un état pathologique du système nerveux central (CNS) définissant la prédisposition à subir des crises épileptiques qui ne sont pas provoquées. Comme l’un des troubles neurologiques les plus courants, l’épilepsie affecte environ 1% de la population mondiale, c’est-à-dire approximativement 80,000 patients en Suisse. Le plus grave de ces symptômes pour les patients épileptiques est le risque de survenue des crises épileptiques, qui se produisent souvent de manière imprévue sans aucun signe avant-coureur ou seulement avec des signes d’avertissement temporaire. Les crises épileptiques peuvent être provoquées par une survenue de potentiel synaptique ou d’autres sources de l’activité épileptique.

En moyenne, quatre crises peuvent être enregistrées par patient par an. Les seuls signes avant-courent pour les crises épileptiques sont généralement des signes neurologiques associés à une épilepsie réfractaire. Les méthodes de diagnostic classique pour l’épilepsie sont basées sur l’interprétation visuelle de l’EEG, qui est une méthode simple mais manquée de sensibilité et de spécificité.

Les principales applications de méthodes d’analyse quantitative de l’EEG (qEEG) consistent à dépister précoce et même anticiper des crises épileptiques, ainsi qu’à localiser le tissu ictogène. Les méthodes qEEG peuvent être classées en fonction du nombre de signaux qui sont étudiés comme sous-entités potentiellement interactives (uni-, bi- ou multivariées). On peut également faire une distinction en fonction du caractère des propriétés du signal ou des effets interactifs. Enfin, on peut examiner une éventuelle relation causale entre les signaux de l’EEG, en d’autres termes, voir s’ils génèrent d’autres signaux ou sont eux-mêmes générés par d’autres signaux.

Dans le présent article sont démontrées à l’appui de l’EEG péri-ictal intracrânien différentes variantes d’analyses qEEG appliquées au département d’épileptologie de l’Université de Berne. Les conclusions cliniques qui peuvent être tirées des résultats sont discutées et l’article met aussi en lumière les limites de même que les perspectives de développement des méthodes d’analyse quantitative.

Mots clés : analyse quantitative de l’EEG, chirurgie épileptique, réseaux

Introduction

Épilepsie est un pathologique state of the central nervous system (CNS) defined by the predisposition to suffer recurrent and unprovoked seizures. As one of the most frequent neurological disorders epilepsy affects roughly 1% of the world population, i.e. approximately 80,000 patients in Switzerland. The most disabling characteristic for epilepsy patients are the seizures, which typically occur suddenly and often without or only with very brief warning signs or symptoms.

In three out of four epilepsy patients seizures can be controlled by anti-seizure drugs [1, 2]. However, in the remainder (approximately 20,000 patients in Switzerland) either combined therapy by multiple drugs is ineffective or the unwanted side effects of the medication cannot be tolerated. For these patients epilepsy surgery [3] is an option that should be evaluated. It is estimated that up to 50% of the target group might benefit from surgical epilepsy therapy [3], which is possible when the seizure onset zone (SOZ) consists of a clearly circumscribed brain area that can be removed without causing unacceptable neurological deficits (i.e. the SOZ is not part of so-called “eloquent cortex”). Epilepsy surgery is a complex intervention requiring interdisciplinary diagnostic workup by neurologists, neuroradiologists, neuropsychologists and neurosurgeons.

Seizures are often considered to be due to pathological changes of synchronization of the electrical activity of large groups of nerve cells. The collective synchronous synaptic potentials and intrinsic currents of nerve cells are measurable by electroencephalography (EEG) [4, 5] on the scalp or inside the cranium under favorable conditions. Most importantly, electrical activity of many neurons must be oriented into the direction of the measurement electrode in order to cause fluctuations of electrical potentials large enough to be detected in several millimeters or centimeters distance. This poses certain limitations, especially on scalp EEG, which is particularly sensitive to events on the top of gyri but detects electrical signals generated in deep brain structures with much reduced sensitivity. Notwithstanding these limitations the EEG continues having high diagnostic value in epilepsy patients.

In pre-surgical evaluation for epilepsy surgery patients suffering from pharmacoresistant focal-onset seizures first undergo continuous scalp video-EEG monitoring (so-called “phase I”) for 1-3 weeks, until several seizures have been recorded. If the clinical and EEG seizure characteristics from phase I are reproducible and in agreement with complementary information as e.g. from high resolution magnetic resonance imaging (MRI), and there are no indications for serious post-surgical neurological deficits the decision about epilepsy surgery may be made already at this stage. If, however, there are inconsistencies, video-EEG monitoring with intracranial electrodes (so-called “phase II”) is required. Here, electrodes are implanted directly onto or into the brain using strip, grid or depth electrodes (Figure 1). Advantages of intracranial EEG (iEEG) is the much better signal to noise ratio and the better spatial resolution (~1cm² as compared to >1cm² for scalp electrodes). However, intracranial electrodes cannot be distributed equally over the whole cortex, thus limiting spatial sampling. Therefore, a good working hypothesis about the localization of the SOZ is required, which can then be tested by a few intracranial electrodes with roughly 30-150 contacts in total. In order to minimize the risk of complications [6], phase II monitoring is often discontinued after several days, thereby potentially limiting the number of recorded seizures to only a few.

The gold standard of EEG interpretation is still visual analysis by trained epileptologists. This classic analysis method basically consists in careful pattern recognition and additional integration of diverse clinical background information. Therefore visual EEG interpretation strongly depends on the experience and at least partly on the subjective interpretation of the individual expert. In addition, visual analysis of iEEG may be made difficult by the large number of signals (up to an order
of magnitude more than for standard scalp EEG). For these reasons visual EEG analysis is increasingly complemented by quantitative EEG (qEEG) analysis, which uses methods developed in mathematics and physics to interpret the EEG more objectively. In the present article qEEG methods are reviewed with special focus on those developed and applied by our research groups.

Currently the main applications of qEEG in epileptology are the following. Early seizure detection [7] may have implications for closed loop intervention systems with the aim of early seizure abortion [8]. Seizure prediction has been a very stimulating goal for the development of qEEG algorithms in the last 15 years. Despite considerable effort, not a single seizure prediction algorithm has so far proven effective in the sense that it outperforms a random predictor in terms of sensitivity and specificity [9-11]. Other – and probably the more promising – applications of qEEG are to reliably localize and delineate the seizure onset zone during pre-surgical diagnostic evaluation.

### Signal characteristics assessed by qEEG

Before elaborating in more detail on different qEEG analysis methods we here list some prominent signal characteristics that may be assessed.

- Epileptic discharges produce fast signals and steep wave forms, which may be strongly localized or propagate over large brain areas. Thus, unraveling high frequencies or steep wave forms may help to localize the origin of epileptic activity.
- In contrast to normal background brain activity epilepto- or ictogenic processes have long been assumed to be associated with strong nonlinearities [12, 13] or even low dimensional deterministic chaos [14]. Consequently, qEEG measures that sensitively and reliably detect nonlinear signal properties may add relevant diagnostic information to visual analysis, which often is strongly biased by linear characteristics (amplitude and frequency distribution, temporal co-evolution of large amplitudes).
- Epileptic brain activity has been conjectured to be more deterministic than normal background activity. Certain qEEG measures quantify the degree of determinism and therefore may help to separate more
deterministic from more noise dominated brain areas or temporal epochs.

- The human brain is one of the most complex known networks. In nerve cells information is integrated via conditional generation of action potentials and information is exchanged via propagation of electrical excitation along axons and dendrites. While the anatomy of the brain network can be investigated non-invasively by magnetic resonance imaging (MRI) techniques, its functional aspects can be revealed by qEEG and fMRI.

- To reconstruct functional networks interrelation measures are used that quantify the degree of association between EEG signals. These measures can or cannot be sensitive to nonlinear effects. In addition, the measures can be asymmetric, thus indicating causal or driver-responder relations.

- For all the signal characteristics mentioned before special attention may be put onto temporal progressions and spatial pathways. Brain areas that are involved early in the epileptic process may play a more important role for seizure generation than those involved late. Similarly, information about critical parts of the network (so-called “hubs”) that spread focal ictal brain activity over larger areas may be considered for planning of epilepsy surgery.

### Systematics of qEEG

Methods of qEEG analysis may be subdivided in several ways. After briefly sketching a systematic classification of qEEG analysis algorithms we give several examples, which will be illustrated using the iEEG of Figure 1.

One possible classification is by the number of EEG signals that are considered as hypothetically independent sub-units (Figure 2). Univariate methods treat every channel as if it was completely isolated from all the other channels. Bivariate methods aim at characterizing the interrelation between pairs of EEG channels. Finally, multivariate methods treat all EEG channels and their interactions as a whole.

This subdivision runs parallel to the assessed spatial scale. Univariate measures inform about the electrical activity beneath a single EEG contact (smallest spatial scale accessible by current iEEG macro-electrodes). In contrast, certain multivariate techniques integrate properties of the whole observed system, therefore assessing the largest accessible spatial scale. Other multivariate techniques inform about processes taking place at intermediate spatial scales.

Another categorization is by linear versus nonlinear methods, which can fall into either of the above mentioned groups. Linear algorithms are suited for description of situations where input and output of a system are proportional, whereas nonlinear algorithms are more general in the sense that no (or less strict) a priori assumptions are made.

Lastly, interrelation measures can be symmetric or directional. Directional interrelation measures allow to assess if one signal is driving or being driven by the other. Symmetric measures assess exclusively the overall degree of interaction.

### Examples for a peri-ictal iEEG recording

#### Univariate measures

The most common univariate, linear qEEG method is power analysis. It is implemented in almost every EEG viewer, where selected pieces of EEG can be decomposed into their spectral content using the Fourier transform. Results of power analysis can either be displayed as the distribution of signal power over the whole frequency range or – in coarser grained manner – as the total power in the classical frequency bands (delta, theta, alpha, beta, gamma). In Figure 3a the power spectra for two epochs of the same iEEG channel of Figure 1b are shown. Power roughly depends on frequency like $P(f) \sim f^{\nu}$ with $1<\nu<2$ [15]. The signal recorded shortly after seizure onset (blue) shows a pronounced peak in high frequencies $60\text{Hz}< f <100\text{Hz}$, which is a typical sign of early ictal EEG activity. Before seizure this peak is absent (red).

During seizures large networks of neurons change the synchronization of their electrical activity. The measurable EEG is affected by showing “epileptiform activity”, which implies either high amplitudes or high frequencies or both. A simple measure that increases in all these situations is the absolute value of the temporal derivative of the EEG signals. Schindler et al. [16, 17] used the EEG “slope” to detect epileptic seizures in a more objective manner than by visual analysis. Similar measures were used in [18, 19]. Figure 3 shows a comparison of the power spectra of original (panel a) signals and their temporal derivative (panel b). Due to elementary properties of the Fourier transform the spectrum of the derivative is much more flat than for the original signals (“spectral whitening”). As compared to the original EEG, where the high frequency peak recorded after seizure onset is suppressed in power by at least one order of magnitude, it constitutes the prominent peak on top of the whitened signals.

For the iEEG of Figure 1 the temporal evolution of the absolute EEG slope as compared to a pre-ictal reference epoch is shown in Figure 4. In panel b “epileptiform” activity is displayed in black and “normal” activity in white. Channel TPL6 recording from the pole of the left temporal lobe shows epileptiform activity more than 30 seconds earlier than the remainder, which follow a clearly visible temporal progression. Also noteworthy is that in contrast to initiation epileptiform activity ceases at the same time in almost all channels.
This becomes clear from the asymmetry in the profile of panel a showing the number of channels recording epileptiform signals. The rise of this number between seconds 30 and 50 is much slower than the abrupt drop near second 80.

In [20] the absolute EEG slope has been used to show that clinically “generalized” seizures not necessarily exhibit epileptiform activity on all channels. Remarkably, this was true despite using intracranial EEG electrodes, which were implanted onto a limited cortex area based on a previous hypothesis about the SOZ. In conclusion, even during “generalized” seizures EEG may not be epileptiform in all brain areas.

The measures discussed so far were all linear. We now briefly address nonlinear univariate measures based on the theory of nonlinear dynamical systems and low dimensional chaos [21, 22]. More comprehensive reviews of EEG applications are given in [23, 14, 24, 25]. According to Takens’ theorem [26] the space in which a nonlinear dynamical system evolves (“phase space”) can in principle be reconstructed from univariate time series. A class of time series analysis methods exploits this theorem and consecutively quantifies properties of the reconstructed attractor. One quantifier that has extensively been applied to qEEG analysis is the correlation dimension and derived measures [27-29], which were used to interpret EEG as showing signs of low dimensional chaos under certain circumstances.
However, after careful re-examination by the same authors, the results of [27] turned out to be not significant [30]. Similar problems were encountered for other analyses.

Another nonlinear way to handle univariate time series is by symbolic analysis. In this class of methods the full information content of the data is coarse grained by deriving a finite (most often a small) number of “symbols” and analyzing their frequency distribution statistically. Consequently, the degree of abstraction of this class of methods is rather high at first sight. On the other hand there is analogy between visual EEG analysis and a special class of symbols, the so called “ordinal patterns”. In both approaches certain wave forms are characterized [31]. To be specific, when analyzing ordinal patterns d consecutive EEG samples are rank ordered and symbols are defined by the sequence of ranks. For instance, for d=3 the symbol “123” (“321”) would indicate a monotonous increase (decrease) and “132” a local maximum. The number of symbols of length d is \[d!=d\cdot(d-1)\cdot...\cdot2\cdot1\]. For Gaussian white noise all symbols are equally likely. In contrast, deterministic dynamics follows an intrinsic rule and the distribution of patterns becomes non-uniform such that in a sample of length \(L\gg d\) some ordinal patterns may not appear at all (“forbidden”). Thus, experimental observation of forbidden ordinal patterns can be interpreted as an indicator of deterministic dynamics [32, 33]. To exclude the possibility of observing forbidden ordinal patterns by chance, comparison with surrogates [34] is mandatory.

In [31] forbidden ordinal patterns have been analyzed for peri-ictal iEEG. An example of this analysis for the iEEG of Figure 1 is given in Figure 5. Before seizure the fraction of forbidden patterns \(n_{fp}\) is in the range 0.5 ... 0.6, indicating that the iEEG signals are much more deterministic than white noise (panel A), which contains no forbidden ordinal patterns. During seizure the fraction of forbidden patterns increases in channels 1 to 16 (contacts on strip electrodes recording from the left temporal lobe) and 41 to 56 (depth electrodes placed in both hippocampal), reflecting increased ictal determinism in these signals. In panel B the time course of channel 6 is compared to the mean over all channels, which undergoes a maximum and then settles at a lower level. Determinism globally increases during seizure and is reduced in the post-ictal time period. The contribution to these changes is not equally distributed.

Another class of symbols are “bit-strings”, i.e. sequences of zeroes and ones [e.g. 00101] that encode certain signal properties as for example whether the EEG amplitude increases (“1”) or decreases (“0”) from one time step to the next. An advantage of bit-strings over ordinal patterns is that for the same length d of used data the space of possible symbols is (much) smaller: 2^d bit-strings as compared to d! for ordinal patterns; for d=5 this difference is 32 vs. 120 and for d=10 it is 1024 vs. 3,628,800. In the context of qEEG of epilepsy patients bit-string (also called “binary”) analysis is still rare.

**Bivariate measures: symmetric**

Next we discuss applications of bivariate interrelation measures to qEEG analysis. One of the most classic quantifiers for data association is Pearson’s cross-correlation coefficient [35]. It evaluates the co-variation of two data sets or time series and tends to values close to zero for uncorrelated data sets. For identical data sets its value is 1 and -1 for data sets that are identical up to a sign, i.e. that are “anti-correlated”. Cross-correlation is best visualized by plotting the second data set (Y) against the first (X) after subtracting the mean and normalizing to unit variance. In Figure 6a this is shown for the neighboring channels TPL6 and TPL7 of the iEEG in Figure 1 (cross-correlation coefficient CC=0.771). For data sets with Gaussian amplitude distribution the lines of equal density are ellipses. Correlation is indicated by ellipses with unequal half axes, such that data points accumulate along one diagonal. In contrast, circular distributions result for uncorrelated data.

Mutual information [36, 37] is another interrelation measure that quantifies the shape of the joint probability distribution of two data sets. It is an entropy based measure for deviations from statistical independence (i.e. data sets whose joint probability distribution is given by the product of the marginal distributions) and can be normalized, such that it assumes values between 0 for independent data and 1 for identical data (up to a sign). In Figure 6b the marginal amplitude histograms are shown for the normalized signals of Figure 6a. Assuming statistical independence the joint probability histogram would be the one of Figure 6c. The considerable deviation of the true joint probability histogram (Figure 6d) from the product rule gives rise to a large mutual information coefficient (normalized mutual information NMI=0.926). The advantage of mutual information over the linear Pearson’s cross-correlation is that it is sensitive to any deviation from the product rule, including curvilinear density distributions as e.g. for the case Y=X^2, the simplest association that is completely missed by cross-correlation (CC=0, NMI=1).

**Bivariate measures: directed**

A variety of interrelation measures aim to quantify not only the overall strength but also the direction of couplings between nonlinear dynamics. These measures include nonlinear Granger causality [38], transfer entropy [39, 37, 40], phase dynamics measures [41], as well as so-called nonlinear interdependence measures ([42] and references therein). The latter operate in the reconstructed phase spaces of the dynamics X and Y (see above). Similar states in X or Y will be spatially
close in the respective phase spaces. Suppose that we have a unidirectional coupling from X to Y. As a result of this coupling, states in the driving dynamics X that are simultaneous to similar states in the driven dynamics Y are on average closer than expected under the assumption of independence. The opposite holds true only to a weaker degree, i.e. closeness in the driving dynamics X not necessarily implies closeness in the driven dynamics Y. Nonlinear interdependence measures exploit this asymmetry to determine the direction of couplings.

Here we show exemplary results for a specific nonlinear interdependence measure, termed \( L \), which was shown to be of higher sensitivity and specificity for directional couplings than a number of related earlier approaches [42]. Figure 7 shows results of a moving window analysis of the peri-ictal recording depicted in Figure 1. During the initial phase of the seizure (16s<t<56s) some off-diagonal elements of the inter-
relation matrix gradually increase. In this epoch the most prominent off-diagonal matrix elements connect channels 1 to 8 (pole of the left temporal lobe, SOZ) with channels 41 to 48 (depth electrode in the left hippocampus). Later (56s < t < 76s) the coupling between the SOZ and temporolateral-basal contacts (channels 9-16) and fronto-central contacts (channels 17-25) becomes more dominant. The deviation from strict symmetry indicates driver-responder relationships. Especially before the seizure the coupling from the SOZ to the depth electrodes (channels 41-56) appears larger than in the opposite direction.

Without going into details an overview of some of the most prominent univariate and bivariate, linear and nonlinear measures that have already been used for qEEG analysis is given in Table 1. For many bivariate measures in addition “partial” versions exist, which account for indirect effects. For example, the value of partial cross-correlation [43] is close to the value of Pearson’s cross-correlation if two signals X and Y are directly interacting. In contrast, partial correlation is much smaller than Pearson’s coefficient if X and Y are interacting via a third signal Z only. Note, the fact that partial interrelation measures only account for observed signals, may be a serious limitation for iEEG, where one is always confronted with incomplete spatial sampling and unobserved activity, which may be responsible for signal associations. Another problem may arise when

---

**Figure 7:** Results of a moving window nonlinear interdependence measure analysis. Each matrix shows results obtained from a window of 20 seconds length. The seizure lasts from t=0s to t=107s. Within individual matrices, high L values in the i-th row and j-th column indicate a strong nonlinear interdependence in the direction from channel with index i to the channel with index j. The asymmetry of these matrices can be interpreted as follows: A positive difference, L(row i, column j) minus L(row j, column i), indicates that the predominant direction of the coupling is from channel with index i to the channel with index j. For a more thorough discussion of the interpretability of these values please refer to Andrzejak et al. [52] and Chicharro & Andrzejak [42].
too many “third” signals $Z_{1} \ldots Z_{N}$ ($N \gg 1$) are offered as possible pathways for indirect interrelation. In this case, the system may be “over-fitted” and direct effects may erroneously be attributed to indirect interaction.

**Multivariate approaches**

Multivariate approaches treat all observed EEG channels and their interactions as a whole. In the following we discuss two classes of multivariate qEEG analysis, both operating on interrelation matrices that were previously defined using bivariate measures. In Figure 8 examples are given for different interrelation matrices evaluated from the same section of intracranial EEG (length two seconds, 2048 temporal samples). The peri-ictal evolution of interrelation matrices (for a directed measure see Figure 7) can be highly complex, making methods for information condensation desirable.

**Multivariate measures based on matrix diagonalization**

Interrelation matrices $\mathbf{C}$ can be interpreted as mappings between vectors in the space spanned by the data channels. Vectors that are mapped onto themselves represent special cases, which can be used to define a mathematically distinguished basis. This basis can be found by solving the matrix equation $\mathbf{C} \mathbf{v} = \lambda \mathbf{v}$. The eigenvalues $\lambda$ can be used to quantify the total interrelation in the system (largest spatial scale accessible by EEG), whereas the eigenvectors $\mathbf{v}$ give information about the contribution of the channels to interrelation patterns (intermediate spatial scale).

For real-valued symmetric matrices $\mathbf{C}$ (as resulting from symmetric interrelation measures, e.g. cross-correlation or mutual information) the eigenvalues are real numbers that can be rank ordered. The sum of all eigenvalues is identical to the sum of the diagonal elements of $\mathbf{C}$, which for normalized measures is equal to the number of channels. A direct consequence is that finite off-diagonal matrix elements $|C_{ij}| > 0$ lead to an increase of large eigenvalues $\lambda$, which is compensated by a decrease of small eigenvalues (“repulsion”; [44]). Relevant information is confined to the repelled eigenvalues and corresponding eigenvectors, whereas the central ones are compatible with Random Matrix Theory (RMT; [45, 44]). First application of eigenvalues of the cross-correlation matrix to peri-ictal iEEG was made by Schindler et al. [46, 17], finding that seizures are not per se highly correlated events. Rather, correlation increases continuously (or even decreases first) and seizures as well as status epilepticus stop when correlation is large.

The value of Pearson’s cross-correlation coefficient is greatly influenced by the signals’ power spectra and the amount of data used for its estimation. In Müller et al. [47] eigenvalue repulsion was exploited to define a measure of “genuine” cross-correlation strength (CCS) to which only significantly repelled eigenvalues of the cross-correlation matrix contribute. The measure of total correlation strength (TCS) integrates all eigenvalues and random correlation strength (RCS) is the same for uncorrelated surrogate data in place of the original data. It was demonstrated that TCS and RCS are sensitive to dynamical changes of the signals’ power spectra even though the interaction was kept constant. In contrast, CCS is almost exclusively sensitive to changes in signal interaction [47]. First application of CCS to epileptic EEG was made in Müller et al. [48]. For focal onset seizures as assessed by scalp EEG it was found that during and after seizure CCS decreases significantly for broadband and low frequency data (below 12.5 Hz). In agreement with recently published results [49] these findings may be interpreted as ictal fragmentation of functional networks.

In Rummel et al. [50] the concept was generalized to TCS, CCS and RCS matrices, with only significant matrix elements retained. An example for the cross-correlation and the CCS matrix of pre-ictal iEEG data is shown in Figures 8a and b, respectively. The CCS matrix is much sparser than the original cross-correlation matrix. Extension to the nonlinear interrelation measure of mutual information was made in Rummel et al. [51]. A combination of linear and nonlinear interrelation measures with univariate and multivariate surrogates [34] enables separation of significantly nonlinear (i.e. interrelation that cannot be explained by linear effects alone) from entirely linear interrelation. In agreement with earlier results [12, 13, 52] preliminary application to intracranial EEG suggests that nonlinearities are more pronounced ictally than interictally and that epileptogenic tissue generates electrical signals with stronger nonlinear characteristics than non-epileptogenic tissue [51].

As discussed earlier, the temporal derivatives of EEG signals may be used to identify channels with epileptiform activity. This suggests to combine temporal differentiation with correlation analysis. In Figure 8c the slope cross-correlation (SCC) matrix is shown and in Figure 8d only significant elements are retained. The average level of correlation is smaller for the temporal derivatives and anti-correlation is almost absent. An advantage of SCC is that fluctuations are much smaller than for Pearson’s coefficient. As a consequence eigenvalues of SCC matrices are much more stable in time [Rummel et al., unpublished]. In Figure 9a the peri-ictal evolution of TCS calculated from the SCC matrix is shown for the iEEG of Figure 1. Pre-ictally the total correlation in the system is remarkably stable. The seizure manifests itself by a pronounced increase of TCS 30 seconds after seizure initiation, i.e. at the time of seizure spreading, cf. Figure 4. In agreement with the findings by Schindler et al. [46, 17] the seizure terminates.
when correlation is largest. In panel b relative changes of the channels’ contribution to the eigenvector $v_M$ corresponding to the largest eigenvalue $\lambda_M$ are displayed. In channels showing early epileptiform activity in Figure 4 the relative contribution to $v_M$ drops significantly (blue), whereas for channels with late onset of epileptiform activity the opposite is true (red). This can be interpreted as a spatial rearrangement of functional interactions within the system, which even persists after seizure termination.

**Multivariate measures based on graph theory**

An alternative multivariate approach is based on graph theory, see [53-56] for reviews. In this context, the signals recorded from EEG electrodes are interpreted as nodes and links between nodes are defined by interrelation measures. Presence or absence of a link between a pair of nodes is defined by the adjacency matrix, which has only elements “0” (no link) or “1” (link present). For binary graphs only the topology of the system is analyzed and therefore the adjacency matrix is the only relevant entity. Based on interrelation matrices the adjacency matrix may most easily be constructed by defining a threshold and setting all elements whose modulus exceeds the threshold to 1 and to 0 otherwise. A more sophisticated procedure is to use link specific thresholds, as e.g. done for determining the elements of the CCS matrix [50] or independently in [57].

Graphs can be analyzed by measures that focus on local and global properties. The most prominent measure for local properties is the **clustering coefficient**. The clustering coefficient of each node X quantifies the fraction of neighbors Y and Z that are also directly connected. Global network properties can be measured by **shortest path lengths or efficiencies**. The efficiency of node X measures how easily all other nodes can be reached from X. The whole network’s efficiency (or clustering coefficient) is the average over all node efficiencies (or clustering coefficients). Another important class of graph measures are the **betweennesses**. Node and link betweennesses quantify the fraction of shortest paths running through a particular node or link. Most graph measures sensitively depend on the link density. Therefore it is advisable to report their values relative to suitably randomized networks.

Measures from graph theory have increasingly been applied to EEG data of epilepsy patients in the last five years, see e.g. [58-62]. We here restrict ourselves to a single illustrative example. The binary graph representation of the CCS matrix of Figure 8b is shown in Figure 10, where all connected nodes are drawn as ellipses and links as lines. All node efficiencies are smaller than those of randomized networks and individual deviations are displayed as gray shadings. The network falls into four sub-graphs, of which two are trivial. The link density is largest in the strip electrode on the pole of the left temporal lobe (TPL) and the depth electrodes (TEL, TER). Interestingly, the connectivity between TPL and TER is high and stems from significantly anti-correlated signals (Figure 8b), whereas TPL and TEL are connected by only a single link, which in consequence has very high link betweenness as well as vulnerability (i.e. the network is significantly changed by removal of this link).

In addition to binary graphs the concept of weighted graphs exists, where the full interrelation matrix is

---

**Table 1:** Overview of prominent univariate and bivariate measures used in qEEG analysis.

<table>
<thead>
<tr>
<th>univariate</th>
<th>bivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>linear</strong></td>
<td><strong>nonlinear</strong></td>
</tr>
<tr>
<td>• power spectrum</td>
<td>• (effective) correlation dimension</td>
</tr>
<tr>
<td>• auto-correlation</td>
<td>• Lyapunov exponents</td>
</tr>
<tr>
<td>• statistical moments of amplitude or power distributions</td>
<td>• Poincaré sections</td>
</tr>
<tr>
<td>• Hjorth mobility</td>
<td>• nonlinear prediction error</td>
</tr>
<tr>
<td>• signal slopes</td>
<td>• local flow</td>
</tr>
<tr>
<td></td>
<td>• algorithmic complexity</td>
</tr>
<tr>
<td></td>
<td>• forbidden ordinal patterns</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
interpreted on basis of graph measures. Also, graphs do not need to be symmetric in the sense that all links are bi-directional. Rather, in directed graphs links can be uni-directional, meaning that information can be transferred only from node X to node Y but not the other way.

Summary and discussion

The development of qEEG analysis methods has been strongly promoted by the goal of seizure prediction over the last 15 years. Despite initial euphoria, so far this problem could not be solved [9-11]. The fact that prediction algorithms at the same time have to be highly sensitive (to avoid that seizures are missed) and specific (to avoid false alarms that expose patients to stress) remains challenging. After all, reliable seizure prediction algorithms have to announce a very large fraction of seizures with sufficient warning time, while the time under false warning must be minimal. It remains questionable whether these requirements can be met in future.

Despite disappointing results with regard to seizure prediction qEEG analysis has generated many promising approaches towards the problems of more objective lateralization and localization of epileptogenic brain areas, some of which have been reviewed in the present article. As illustrated at the example of a peri-ictal iEEG recording, the ictal dynamics of many complementary qEEG measures characterize the same brain region as epileptogenic in this patient (pole of the left temporal lobe, iEEG channels TPL5-TPL7, see Figure 1). After surgical removal of this brain region the patient has become seizure free for more than two and a half years.

Regarding univariate properties the power spectrum and absolute slope reveal high frequency components on these channels, which are much less pronounced in the remainder (Figures 3 and 4). A symbolic dynamic approach counting forbidden ordinal patterns shows

![Figure 8: (color) Examples of different interrelation matrices for the same pre-ictal iEEG epoch of two seconds length. a) cross-correlation matrix, b) CCS matrix of [50], c) slope cross-correlation matrix of [53], d) CCS matrix based on slope cross-correlation.](image-url)
Quantitative Analysis of Peri-Ictal Multi-Channel EEG

C. Rummel, R. G. Andrzejak, K. Schindler

First ictal changes on the same channels (Figure 5). Similarly, a bivariate directed measure detects the earliest and most prominent off-diagonal interrelations between channels 1-8 and the ipsilateral depth electrode (channels 41-48, see Figure 7). Multivariate quantifiers localize the first and most pronounced alterations in signal interaction to the pole of the left temporal lobe (Figure 9). Interestingly, correlation of iEEG slopes of these channels decreases significantly at seizure onset, i.e. in a region and epoch where neuronal cooperativity (as e.g. assessed by large signal power in high frequency components or large signal slopes) increases. This indicates a significant reorganization of functional networks in the course of epileptic seizures [49]. Measures based on graph theory have also been briefly illustrated (Figure 10).

Notwithstanding the achievements of qEEG analysis tools, there remain several limitations and pitfalls. As EEG measures electric potential differences, no absolute values can be given. Rather, all results of qEEG analysis depend on the chosen reference electrode or montage. For some qEEG measures this influence has...
been studied systematically [63-65]. A general advice for an “optimal” reference is impossible. Rather, references that obviously influence a qEEG measure should be avoided and in case of doubt analysis should be repeated using different montages. Another caveat that is often discussed in regard to EEG interrelation measures is “volume conduction”, i.e. the fact that electric potentials are effective also at distances and in free space. Due to the relatively small size of human brains (diameter <20cm) volume conduction propagates through the whole brain in less than a nanosecond, i.e. instantaneously on time scales measurable by EEG (typical time scale: milliseconds). Therefore, one possibility to suppress spurious interrelation due to this effect is by looking only at finite temporal lags between signals. One has to be aware, however, that besides volume conduction this rather crude filtering may eliminate “true” interactions taking place at zero lag, too. In addition, electric fields may well have physiologic effects, too [66].

Nonlinear time series analysis of neurophysiologic data [22, 24, 25] has long been “en vogue”. Later, the importance of nonlinearity in neurophysiological time series and especially the capability of measures to detect nonlinearities reliably from short and noisy experimental data have been challenged. Comparing the sensitivity and specificity of various bivariate interrelation measures for model data, it was recently found that linear measures perform equally well or even better than nonlinear measures — even if the signals or the interrelation were indeed nonlinear [67-69]. However, there are indications that a separation of significantly nonlinear from entirely linear interrelation may reveal useful additional information. For a collection of univariate and bivariate measures it has been found that correction of nonlinear qEEG measures by surrogates with identical linear properties increases the ability for localization of the SOZ [13, 52]. A first multivariate study carried out in [51], finding indications that localization of the SOZ may be supported along similar lines has been carried out in [51], finding indications that a separation of significantly nonlinear from entirely linear interrelation may reveal useful additional information. For a collection of univariate and bivariate measures it has been found that correction of nonlinear qEEG measures by surrogates with identical linear properties increases the ability for localization of the SOZ [13, 52]. A first multivariate study carried out in [51], finding indications that localization of the SOZ may be supported along similar lines has been carried out in [51], finding indications that a separation of significantly nonlinear from entirely linear interrelation may reveal useful additional information. For a collection of univariate and bivariate measures it has been found that correction of nonlinear qEEG measures by surrogates with identical linear properties increases the ability for localization of the SOZ [13, 52]. A first multivariate study carried out in [51], finding indications that localization of the SOZ may be supported along similar lines has been carried out in [51], finding indications that a separation of significantly nonlinear from entirely linear interrelation may reveal useful additional information. For a collection of univariate and bivariate measures it has been found that correction of nonlinear qEEG measures by surrogates with identical linear properties increases the ability for localization of the SOZ [13, 52]. A first multivariate study carried out in [51], finding indications that localization of the SOZ may be supported along similar lines has been carried out in [51], finding indications that a separation of significantly nonlinear from entirely linear interrelation may reveal useful additional information. For a collection of univariate and bivariate measures it has been found that correction of nonlinear qEEG measures by surrogates with identical linear properties increases the ability for localization of the SOZ [13, 52]. A first multivariate study carried out in [51], finding indications that localization of the SOZ may be supported along similar lines has been carried out in [51], finding indications that a separation of significantly nonlinear from entirely linear interrelation may reveal useful additional information. For a collection of univariate and bivariate measures it has been found that correction of nonlinear qEEG measures by surrogates with identical linear properties increases the ability for localization of the SOZ [13, 52]. A first multivariate study carried out in [51], finding indications that localization of the SOZ may be supported along similar lines has been carried out in [51], finding indications that a separation of significantly nonlinear from entirely linear interrelation may reveal useful additional information. For a collection of univariate and bivariate measures it has been found that correction of nonlinear qEEG measures by surrogates with identical linear properties increases the ability for localization of the SOZ [13, 52]. A first multivariate study carried out in [51], finding indications that localization of the SOZ may be supported along similar lines has been carried out in [51], finding indications that a separation of significantly nonlinear from entirely linear interrelation may reveal useful additional information. For a collection of univariate and bivariate measures it has been found that correction of nonlinear qEEG measures by surrogates with identical linear properties increases the ability for localization of the SOZ [13, 52]. A first multivariate study carried out in [51], finding indications that localization of the SOZ may be supported along similar lines has been carried out in [51], finding indications that a separation of significantly nonlinear from entirely linear interrelation may reveal useful additional information. For a collection of univariate and bivariate measures it has been found that correction of nonlinear qEEG measures by surrogates with identical linear properties increases the ability for localization of the SOZ [13, 52]. A first multivariate study carried out in [51], finding indications that localization of the SOZ may be supported along similar lines has been carried out in [51], finding indications that a separation of significantly nonlinear from entirely linear interrelation may reveal useful additional information. For a collection of univariate and bivariate measures it has been found that correction of nonlinear qEEG measures by surrogates with identical linear properties increases the ability for localization of the SOZ [13, 52]. A first multivariate study carried out in [51], finding indications that localization of the SOZ may be supported along similar lines has been carried out in [51], finding indications that a separation of significantly nonlinear from entirely linear interrelation may reveal useful additional information. For a collection of univariate and bivariate measures it has been found that correction of nonlinear qEEG measures by surrogates with identical linear properties increases the ability for localization of the SOZ [13, 52].

Nonlinear time series analysis of neurophysiologic data [22, 24, 25] has long been “en vogue”. Later, the importance of nonlinearity in neurophysiological time series and especially the capability of measures to detect nonlinear properties reliably from short and noisy experimental data have been challenged. Comparing the sensitivity and specificity of various bivariate interrelation measures for model data, it was recently found that linear measures perform equally well or even better than nonlinear measures — even if the signals or the interrelation were indeed nonlinear [67-69]. However, there are indications that a separation of significantly nonlinear from entirely linear interrelation may reveal useful additional information. For a collection of univariate and bivariate measures it has been found that correction of nonlinear qEEG measures by surrogates with identical linear properties increases the ability for localization of the SOZ [13, 52]. A first multivariate study along similar lines has been carried out in [51], finding indications that localization of the SOZ may be supported by searching for brain areas with increased significant nonlinearities.

In the last years application of so-called “micro electrodes” in parallel to normal iEEG electrodes has become possible. These micro electrodes record the discharges of small groups of neurons or even of single units and can be used to study high frequency oscillations, see article by J. Jacobs in this issue. Recently a unified approach to detect directional interrelations between pairs of spike time series, pairs of time continuous signals as well as between pairings of spike time series with time continuous signals was proposed by Andrzejak and Kreuz [70]. This approach promises to be of high value for the study of micro electrode recordings of neuronal spiking and local field potentials. Without doubt it is necessary to further extend such qEEG tools to address the specific characteristics of these signals as well as of the combination of micro and macro electrodes.

Future developments of qEEG analysis will also include integration with other modalities, such as fMRI (see article by M. Hauf et al. in this issue) or functional near-infrared spectroscopy (fNIRS), both assessing the hemodynamic response of cerebral vessels. fNIRS is a noninvasive technique, whose spatial and temporal resolution is comparable with scalp EEG. In contrast to fMRI interaction with EEG is negligible and head motion is tolerated well. This makes combined EEG-fNIRS a promising tool for investigating of normal and pathological brain function.

Despite the considerable progress that has been achieved in development of qEEG analysis techniques, it certainly has not yet been integrated into clinical routine. In the future, efforts will have to be increased to close the gap between research applications and everyday clinical EEG assessment. Furthermore, it is conceivable — and maybe desirable — that with the help of a variety of qEEG analysis techniques epilepsy surgery of the future will increasingly consist in targeted disconnection of epileptic networks rather than in a complete removal of the SOZ.

References
11. Quantitative Analysis of Peri-Ictal Multi-Channel EEG


52. Andrezejak RG, Chicharro D, Lehnhertz K, Mormann F. Using bivariate signal analysis to characterize the epileptic focus: The benefit of surrogates. Phys Rev 2011; 83: 046203


64. Guevara R, Pérez Velazquez JI, Nenadovic V et al. Phase synchronization measurements using electroencephalographic recordings – What can we...


70. Andrzejak RG, Kreuz T. Characterizing unidirectional couplings between point processes and flows. Europhys Lett 2011; 96: 50012

Address for correspondence:
Dr. Christian Rummel
Support Center for Advanced Neuroimaging,
Institute for Diagnostic and Interventional Neuroradiology,
Inselspital,
CH 3010 Bern
Tel. 0041 31 6328038
Fax 0041 31 6324872
crummel@web.de