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The Impact of EEG/MEG Signal Processing and Modeling in the Diagnostic and Management of Epilepsy

Fernando H. Lopes da Silva

Clinical Application Review

Abstract—This overview covers recent advances in the field of EEG/MEG signal processing and modeling in epilepsy regarding both interictal and ictal phenomena. In the first part, the main methods used in the analysis of interictal EEG/MEG epileptiform spikes are presented and discussed. Source and volume conductor models are passed in review, namely the equivalent dipole source concept, the requirements for adequate time and spatial sampling, the question of how to validate source solutions, particularly by comparing solutions obtained using scalp and intracranial EEG signals, EEG & MEG data, or EEG simultaneously recorded with fMRI (BOLD signals). In the second part, methods used for the characterization of seizures are considered, namely dipolar modeling of spikes at seizure onset, decomposition of seizure EEG signals into sets of orthogonal spatio-temporal components, and also methods (linear and nonlinear) of estimating seizure propagation. In the third part, the crucial issue of how the transition between interictal and seizure activity takes place is examined. In particular the vicissitudes of the efforts along the road to seizure prediction are shortly reviewed. It is argued that this question can be reduced to the problem of estimating the excitability state of neuronal populations in the course of time as a seizure approaches. The value of active probing methods in contrast with passive analytical methods is emphasized. In the fourth part modeling aspects are considered in the light of two special kinds of epilepsies, absences characterized by spike-and-wave discharges and mesial temporal lobe epilepsy. These two types correspond to different scenarios regarding the transition to epileptic seizures, namely the former is a case of a jump transition and the latter is a typical case of gradual transition. In conclusion, the necessity of developing comprehensive computational models of epileptic seizures is emphasized.

Index Terms—EEG, epilepsy, interictal, MEG, seizure prediction, seizures, signal processing, source modeling, volume conductor.

I. INTRODUCTION

A. Interictal and Ictal Phenomena

IN AN EPILEPSY diagnosis, we have to distinguish between two main kinds of epileptic phenomena: *ictal phenomena*, i.e., epileptiform seizures, and *interictal phenomena*,

i.e., transient events that occur in-between seizures. The main interest of the clinical neurophysiologist is twofold: in the *first* instance, it is to *detect the occurrence* of epileptiform phenomena since these are important elements to establish a diagnosis of epilepsy, along with clinical and other information; *second*, it is important to *estimate the localization and the extent* of the brain areas which are responsible for the generation of these phenomena. Many algorithms performing electroencephalogram (EEG) signal processing, have been developed to extract information pertaining to interictal and ictal epileptiform discharges in order to provide the clinical neurophysiologist with tools that may facilitate a more accurate diagnosis, which, in turn, should contribute to improve the management of the patients. The paramount area of clinical interest with respect to the application of EEG signal analysis, however, is that of the presurgical evaluation of epileptic patients, where obtaining answers to questions regarding the localization of epileptiform activities within the brain is crucial. Nonetheless, it is also of clinical importance to develop analytical tools that may yield relevant data with respect to scalp EEG/magnetoencephalography (MEG) records since the latter are noninvasive and can be obtained safely, rather easily in an outpatient environment.

We first pass in review a few general definitions used in the field of epileptology in order to clarify some concepts that are relevant for EEG/MEG signal processing in the diagnostic and management of epileptic patients.

In general, while performing presurgical evaluation of these patients six cortical zones are considered: the *irritative zone*, the *seizure onset zone*, the *symptomatogenic zone*, the *epileptogenic lesion*, the *epileptogenic zone*, and the *functional deficit zone* [126]. The determination of the *symptomatogenic* and the *functional deficit zones* is mainly made on the basis of clinical and neuropsychological information. The *epileptogenic lesion* is mainly determined by means of imaging techniques [magnetic resonance imaging (MRI), single photon emission computerized tomography (SPECT), or positron emission tomography (PET)]. The *epileptogenic zone*, is defined as the minimum amount of cortex that must be resected (inactivated or completely disconnected) to produce seizure freedom is a theoretical concept which currently can only be validated post-surgery.

The two zones that have to be defined mainly on neurophysiological grounds are the *irritative* and the *seizure-onset*

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zones. It is with respect to the estimation of these two zones that EEG/MEG signal processing may yield the most relevant contribution. Therefore, they are the main targets of this review.

- The *seizure-onset zone* is the area of cortex from which clinical seizures (i.e., ictal activities) are initiated. This area is determined primarily by EEG (invasive and noninvasive), but ictal SPECT and to a lesser degree functional MRI (fMRI) and magnetoencephalography (MEG) may contribute. Regarding the *seizure-onset zone*, it is necessary to define as precisely as possible what is meant by area of seizure onset. In terms of EEG signals this area is characterized by fast synchronizing discharges (low-voltage rapid activity or sustained fast discharges of spikes), with variable frequencies and patterns.
- The *irritative zone* is the area of cortex which generates interictal spikes. This area is estimated by EEG (invasive and noninvasive) and/or MEG. fMRI may be of assistance in defining the volume of tissue that generates *interictal spikes*, since it may reveal brain areas showing changes in metabolism and blood flow associated with epileptiform spikes seen in the EEG [37]. One classic issue is to detect whether *interictal spikes* are generated within or outside the epileptogenic zone; Penfield and Jasper [95] coined the colorful terms “red spikes” for the interictal spikes originating from the cortex that had to be resected = epileptogenic zone, and “green spikes” those originating from cortex that did not have to be resected. In this context, the irritative zone will not overlap with the *epileptogenic zone*. The identification of the cortical areas involved in producing *interictal spikes* is often complicated, since one is frequently faced with abundant paroxysmal activities, the firing pattern, and location of which fluctuate greatly. Indeed it is also important to estimate co-activated brain areas during interictal spikes, in order to determine the extent of neuronal networks involved in this epileptiform activity.
- We should note that besides this irritative activity an alteration of background EEG or MEG activity, has also been noted in epileptic cortical areas. Using MEG, Gallen *et al.* [27] recorded abnormal low-frequency (magnetic) activity (ALFMA) using magnetic source imaging.
- In epileptic patients who showed no interictal spikes, the detection of ALFMA showed a 48.5% specificity with respect to the presumed epileptogenic zone.
- Recently special attention has been paid to the occurrence of high-frequency oscillations (*fast-ripples at 250 and 500 Hz*) associated with epileptiform spike activity in human hippocampus and entorhinal cortex of patients with mesial temporal lobe epilepsy using wideband EEG signals recorded with microelectrodes during sleep [12], [13], [105], as found also in the rat model of temporal lobe epilepsy [11]. Recently, researchers have investigated systematically whether these high-frequency oscillations could also be recorded by means of standard indwelling macroelectrodes, commonly used in presurgical evaluation of pharmaco-resistant epileptic patients. Urrestarazu *et al.* [110] recorded high-frequency oscillations using intracranial macroelectrodes in a subgroup of patients with focal epilepsy during slow-wave sleep, and charac-

terized them by way of continuous-time wavelet analysis, as fast oscillations at frequencies higher than 250 Hz; these oscillations appear to have a higher rate and higher power in the seizure onset zone. Worrell *et al.* [125] noted that fast ripples were most often recorded on a single microelectrodes, while macroelectrodes recorded mainly lower oscillations at frequencies about 116 Hz, and concluded that fast ripples are primarily generated by highly localized neuronal populations, and can preferably be detected by appropriately placed microelectrodes. Be as it may, there is a growing interest in exploring whether these fast-ripple activities may be used to help localize the epileptogenic zone but there is a problem of spatial sampling to be solved, since the neuronal foci of fast ripples appear to be rather small and not homogeneously distributed throughout the hippocampal formation. The problem of spatial sampling cannot be ignored, particularly with respect to the acquisition of depth recordings from cerebral structures.

II. INTERICTAL EEG AND MEG EPILEPTIFORM SPIKES: SPIKE CLUSTERING, SOURCE AND VOLUME CONDUCTOR MODELS AND LOCALIZATION ESTIMATES

The impact of EEG/MEG signal processing and modeling with respect to interictal activity, or epileptiform transients, and thus to the characterization of the irritative zone, can be considered according to two dimensions: spatial and temporal. The spatial approach focus on the identification of brain areas responsible for the occurrence of epileptiform transients and their topographic properties (localization, extent, orientation); the temporal approach targets on the evolution of the occurrence of these transients as time series.

In any case, the problem of localizing sources of epileptiform spikes within the brain based on scalp EEG or MEG recordings implies the choice of appropriate *source and volume conductor models*.

A. The Equivalent Dipole Source Concept

The most common source model is the dipole layer or *equivalent dipole*. The latter is justified on account of basic data from neurophysiology and neuroanatomy, since the main neuronal sources of epileptiform spikes consist of cortical patches having a sink-source laminar distribution across the cortical depth. In this way, they form open fields in the classic sense introduced by Lorente de N6 [72]. As shown in an elegant basic study by Murakami and Okada *et al.* [85], layer V and layer II/III pyramidal cells have an open-field configuration and are capable of producing strong current dipoles, whereas the layer IV spiny stellate and layer III aspiny stellate cell with closed-field configurations produced weaker current dipoles.

B. Requirements for Time and Spatial Sampling

We have to note that in order to apply EEG/MEG analytical tools to detect this kind of activity one has to perform a proper sampling both in time and space taking into consideration that these events have high-frequency temporal and spatial components and that their occurrence may involve very limited extent of the cortex. In general, we may state that to achieve an accept-

able time resolution one should not sample the signals below 625 Hz [122]. Regarding the spatial resolution, we should realize that some spikes may be accounted for by a radial dipole localized in the crown of a cortical gyrus. In this case, if one uses the traditional 10–20 system (interelectrode distance of about 4.5 cm), there will be a spatial aliasing error of 6% [68]. To reduce this error to the more adequate level of 1%, one must reduce the interelectrode distance to 3.2 cm, which corresponds to placing at least 64 electrodes over the head. Gevins and Bressler [28] indicate that sampling with 128 electrodes (interelectrode distance of 2.25 cm) may be indicated in some cases. A comprehensive system, called the 10% system, includes electrodes halfway between each of the principal 10–20 system electrodes [17], [87]. Electroencephalographic signals recorded according to such a system using a high spatial sampling frequency are called *high-resolution EEGs*. Nowadays, several systems use 256 electrodes to obtain a finer sampling of the electrical activity at the scalp [15], [101].

Recordings under these conditions are important for an appropriate application of signal analysis methods to EEG or MEG signals with the objective of estimating the topographical properties of epileptiform spikes as indicated above.

To perform the analysis of sources of various kinds of cortical phenomena, including epileptiform spikes, using high-resolution EEGs Gevins and collaborators [29] introduced a deblurring operation, i.e., a method to minimize the blur distortion that takes place in the transfer from the cortical surface to the scalp, using a realistic finite-element model of the MRI of the subject's head. According to this approach, the scalp and skull are approximated by tetrahedral finite elements having the physical properties characteristic of the different layers of the head, and the algorithm searches for the optimal potential distribution at the cortical surface that provides the best-fit forward solution to the measured scalp distribution, using an appropriate volume conductor model (see below). In essence the deblurring operation consists in a high-pass filtering operation in the spatial domain [122].

C. From Topographical Maps to Source Modeling

The simplest and most general form of analysis of epileptiform transients is to perform topographical maps of the transients. The case of epileptiform spikes that are characteristic of Benign Rolandic Epilepsy of Childhood (BREC) is illustrative of the impact that EEG/MEG analysis has had in providing insight into the abnormal neuronal processes underlying these events. In these cases there is a focus of epileptiform transients in and around the Rolandic region. Whether or not the spikes characteristic of Rolandic epilepsy can be described by a single or multiple dipolar sources [6], [94], [114], [115] appears to depend on the nature of the epileptic condition, but is also affected by the analytical methodology applied. Indeed, the case of Rolandic spikes is exemplary of how to perform *source modeling* of epileptiform spikes, since in this case the sources are assumed to be localized in a well-defined region around the lower part of the Rolandic sulcus [46].

Clinical neurophysiologists are naturally interested in going further than topographical mapping in searching for the sources

of epileptiform activity. They wish, namely, to localize the corresponding sources within the brain and in relation to brain anatomy, i.e., to find the inverse solution based on scalp topographical maps of EEG or MEG activity. Source localization, however, is confronted with the general problem that the inverse problem is ill-posed, and it does not have a unique solution. Therefore, constraints have to be introduced in order to estimate possible solutions. Furthermore, a substantial amount of data is needed to improve the signal-to-noise ratio of a single EEG/MEG event that, in general, is too poor for source localizations.

The initial analyses were carried out using a relatively limited number of electrodes and simple volume conductor models, and the results obtained at that stage were rather limited and variable. The availability of more powerful techniques using higher spatial sampling rates (EEG and MEG recordings), and of algorithms by means of which realistic models of the head based on high-resolution MRI can be constructed, opened up a more comprehensive analysis of these epileptiform phenomena.

A problem that has to be tackled in these kind of analyses is that epileptiform spikes usually display poor signal-to-noise ratio and a considerable variety of morphological features even recorded from the same patient. This diversity reflects that spikes may originate in different cortical areas. This heterogeneity precludes the use of simple averaging to increase signal-to-ratio. Therefore, it is advisable to perform, as a first stage in these investigations, a *cluster analysis* of the set of population spikes, before averaging those events that belong to each cluster. These “cluster averages” can then be used to estimate the corresponding intracerebral dipolar sources. This methodology was applied in a MEG study of epileptiform spikes in patients with localization-related epilepsy [116]. For each patient, distinct spike clusters, or subpopulations were identified corresponding to clearly different topographical field maps (Fig. 1). In these cases, the application of the inverse solution algorithm to the selected spike “cluster averages” led to estimate source solutions in agreement with the estimated location of seizure onset zones and of the epileptogenic structural lesions.

The equivalent dipole model has been considered unsatisfactory since it carries the suggestion that the brain area responsible for the epileptiform spike would be a well circumscribed cortical area. This is, of course, not so and indeed it is important to note that the localization of the equivalent dipole indicates roughly the maximum of a relatively widespread intracerebral field the activity of which is reflected in the spatial distribution of the epileptiform spike.

In this context, it is important to take the study of Kobayashi *et al.* [54] into consideration, since these authors analyzed the accuracy of representing cortical sources of epileptiform spikes using the single-dipole model, by way of realistic simulations. They report that dipoles estimated from scalp spikes arising from cortical sources of 6 cm² were inconsistent. Extension of the source area was associated with increase of scalp potential amplitude, and an increase in the consistency of the estimated dipoles; however, when the source was very large, the dipoles appeared at misleading locations. Therefore, these authors conclude that “pitfalls in dipole source localization are caused by

Fig. 1. Top: Topographical maps of the average magnetic fields of five epileptiform spike clusters found in patient C, and the corresponding overlays of the magnetic fields at the time of the marker, indicated by the red dashed vertical line in the overlays recorded from all sensors. Bottom: Position of equivalent dipoles fitted to the average MEG spikes of clusters 1 and 2 combined, and also for cluster 5. Clusters 3 and 4 are not shown since the equivalent dipolar sources had residual errors $>10\%$. The boundary of the lesion in the right frontal lobe is marked by the dotted line. (Adapted with permission from Van 't Ent *et al.*, *Clin. Neurophysiol.*, vol. 114, no. 10, pp. 1948-1962, Oct. 2003).

the procedure of fitting the simplistic dipole model to real cortical sources with spatial extent and complex configuration,”

Indeed the dipolar source model has the charm of being simple and straightforward but one has to be very careful in its application and even more in the interpretation of the results. The application is limited to those cases where the extent of the putative cortical sources is circumscribed, and the signal-to-noise ratio is good. A successful approach is the following: 1) the spatio-temporal set of spike recordings is decomposed in clusters, using for example Ward's hierarchical clustering and the “moving average quality control rule” [78], [79] as done by van 't Ent *et al.* [116]; 2) the clusters are appropriately averaged (e.g., taking care of the necessary alignment) to improve the signal-to-noise ratio; 3) the inverse dipolar solution is estimated for the relevant clusters' average; and 4) the solutions are displayed in the appropriate number of sequential slices of the MRI scans (not just one single MRI scan) of the same subject.

In order to improve the estimation and display of source solutions, and to avoid the pitfalls of dipolar modeling in case the sources are too complex, other methods have been developed that have the common property of estimating distributed sources in the brain, namely by directly computing the current distribution throughout the full brain volume, assuming that neighboring neuronal populations are simultaneously and syn-

chronously activated. One of the methods of this kind that is widely used is called low resolution electromagnetic tomography (LORETA) [56], [93]. LORETA selects the smoothest of all possible 3-D current distributions and, in this way, it introduces a certain amount of spatial dispersion.

We cannot describe all different methods that have been proposed with the aim of localizing distributed sources in general and epileptiform spikes in particular. In a comprehensive study of Grova *et al.* [39] compared distributed source localization methods and used realistic simulations of EEG epileptiform spikes, at different anatomical locations and spatial extents. Six source localization methods were evaluated: the minimum norm, the minimum norm weighted by multivariate source prelocalization (MSP), cortical LORETA with or without additional minimum norm regularization, and two derivations of the maximum entropy on the mean (MEM) approach. These authors concluded that LORETA-based and MEM-based methods were able to accurately recover sources of different spatial extents, with the exception of sources in temporo-mesial and fronto-mesial regions and “that one should always take into account the results from different localization methods when analyzing real interictal spikes.” This field is, however, very dynamic and all the time new methods are proposed.

Currently, two particularly interesting developments should be mentioned: Ou *et al.* [91] proposed a novel distributed spatio-

temporal EEG/MEG $l(1)l(2)$ -norm inverse solver for estimating the sources of EEG/MEG signals. In this approach, a $l(1)$ -norm spatial model is integrated with a temporal model of the source signals in order to avoid unstable activation patterns. Validation with simulated and real MEG data shows that the proposed solver yields source time course estimates qualitatively similar to those obtained using equivalent dipole fitting. An advantage is that using this method it is not necessary to specify the number of dipole sources in advance, and that it yields fewer false positives and a better representation of the source locations than the conventional $l(2)$ minimum-norm estimates. Another novel method was introduced by Haufe *et al.* [43] for inverse imaging of vector fields (Focal Vector Field Reconstruction), who showed that this method was successful in finding the joint localization of 2–3 simulated dipoles, what, according to these authors was not the case for other methods because the solutions were either too smooth (LORETA, Minimum $l(1)$ -norm) or too scattered (Minimum $l(2)$ -norm). There are as yet, however, no applications published regarding epileptiform spikes.

D. Analysis of Propagation Patterns

In exploring the brain to find areas of irritative activity using intracerebral recordings, Chauvel's group developed a quantitative method [10], first, to automatically detect epileptiform spikes in various brain areas and, second, to estimate the degree of association between spikes recorded in these areas. Groups of brain areas displaying spikes within the same time window were named subsets of co-activated structures (SCASs). These authors applied the method to long duration interictal recordings in patients with mesial temporal lobe epilepsy (MTLE) and were able to find significant relationships between epileptiform activity occurring in anatomically separated brain areas, particularly those involving the two functional systems of the temporal lobe, the mesial and the lateral system. Similarly, topographical relations of EEG epileptiform transients recorded at the scalp were determined based on estimating the degree of time association of those transients recorded in pairs of derivations, or in 3 (triads), 4 (tetrads) or more derivations using the χ^2 statistic. In this way, spatial displays can be made that show the location of the dominant irritative area and the spread of epileptiform activity over the head. [40].

E. Testing the Validity of Source Solutions

Given a solution of an inverse problem in EEG/MEG, the question remains of determining the validity of the estimated source, since the latter depends always on the process of estimation.

Three kinds of validation approaches may be distinguished: one is based on: a) comparisons of solutions obtained based on scalp EEG/MEG data with data obtained through direct recordings with indwelling electrodes in the brain; the other two are based on comparisons between the results of different methods: b) EEG and MEG; c) EEG or MEG and fMRI.

a) A carefully conducted comparison between equivalent dipolar sources estimated from scalp EEG, or MEG, recordings and intraoperative electrocorticographical observations used as the standard [60] yield a correct localization of the source to the temporal lobe in four

out of five MEG and three out of eight EEG recordings. The best correlation between EEG or MEG findings and intracranial electrocorticography findings was between horizontal EEG dipole orientation and prominent neocortical spiking.

b) Several studies used both modalities, EEG and MEG to characterize epileptiform spikes. In general, the idea that one may deduce from these studies is, as pointed out by Baumgartner [7], that the combination of EEG and MEG provides useful information for the localization of epileptiform activity spikes which may not be obtained with either technique alone. A recent study by Pataria *et al.* [94] using simultaneously recorded EEG and MEG in patients with Benign Rolandic Epilepsy of Childhood (BREC) reported that simultaneous EEG and MEG provide comprehensive information on functional organization of spikes in BREC. It has been shown that EEG and MEG spikes that occur at the same time differ in a number of quantitative parameters, with respect to duration, sharpness, and shape, and thus the spikes recorded in EEG and MEG reflect different properties of the sources, namely, the orientation of the dipolar sources regarding the cortical surface (crown of a gyrus or bank of a sulcus) [21]. Taking also into consideration that both modalities are differently affected by the properties of the tissues between brain and scalp and may have different signal-to-noise ratios, it is likely that the two modalities yield complementary information, what may improve estimating solutions of the inverse problem.

Recently, Molins *et al.* [80] showed using a three-compartment boundary-element forward model based on structural MRI scans of four subjects higher spatial resolution in EEG+MEG as compared with MEG. The effect was apparent in all source locations, with increased magnitude for deep areas such as the cingulate cortex. This demonstrates the enhanced power of estimating inverse solutions using combine EEG and MEG data.

c) With the technical possibility of measuring simultaneously EEG and fMRI, several studies were performed with the aim of finding whether the combination of these techniques could be of help in improving solutions of the inverse problem. This problem, however, is not trivial since the time scales at which an EEG epileptiform spike takes place and the possibly associated change in hemodynamic response, as estimated using fMRI BOLD signal, are very different. A further problem is that little is known about the BOLD response to an epileptiform spike [9]. Another issue is that the set of spikes is not homogeneous and that these must first be clustered in order to form more homogenous sets, as indicated above and described in van 't Ent [116] and adapted to the issue of EEG-fMRI correlations by Liston *et al.* [65]. The latter authors implemented a semi-automated system, based on the spatio-temporal clustering of EEG events and each cluster of epileptiform spikes was modeled separately for the purpose of correlating with the fMRI BOLD signal. The authors conclude that automated classification of epileptiform spikes can result in more objective fMRI models

of these transients. Similarly, the fMRI data need also to be split in different components since not all aspects of the BOLD signal are relevant for the correlation with the epileptiform activity. This was done by Rodionov *et al.* [102] who decomposed the BOLD signals using principal component analysis (ICA) and found that some components correlated best with the EEG epileptiform activity as given by the general linear model (GLM).

F. Volume Conductor Models

As stated above, to tackle the problem of estimating the ill-posed inverse solutions applied to epileptiform spikes one has not only to choose a source model but also the appropriate model of the volume conductor. At early times, the head was commonly approximated as a sphere what is, of course, not realistic. With the generalization of the use of structural MRI; realistic models of the head became common practice. Therefore, there is a need to know the head and brain shapes, thickness of the skull and other tissue layers to improve the quality and accuracy of the estimates of inverse solutions. Accordingly, Nunez *et al.* [86] discussed the intricacies of mathematical models of the skull and brain volumes, and Gevins *et al.* [29] used corrected and aligned MRI images to recreate a realistic head model. The possibility of using detailed MRI images to model the gyral pattern amenable to mathematical solutions has been explored [2].

A general problem in estimating relevant solutions of the inverse problem in the case that one uses EEG data is that the electrical properties of the tissues (e.g., resistivity) between the scalp electrodes and the brain sources should be known. This is much less important in the case of MEG data since the tissue layers of the head are transparent for magnetic fields. The electrical resistivity values used in the literature show a wide variation, and were based on *in vitro* or animal measurements. Recently, several studies attempted to estimate *in vivo* the electrical resistivities of the surrounding and including the brain [23], [26], [47], [89], [109]. Based on *in vivo* electrical impedance tomography (EIT), our group measured the electrical resistivities of brain, skull, and scalp in six different subjects, using realistic models of the head, and the boundary element method to solve the forward problem [32]. The results demonstrate that the ratio between the resistivity of the skull and the brain varies among subjects from 20 and 50, and thus it differs considerably from the commonly accepted value of 80. These experimental results show also that for a more reliable estimate of the sources of epileptiform spikes, it is important to use a realistic model of the head including values of resistivities directly estimated for each subject using EIT.

III. CHARACTERIZATION OF SEIZURES: ONSET AREAS AND PROPAGATION PATTERNS

In this section, we consider two main aspects where analytical approaches have contributed to obtain a better understanding of where in the brain the sources of seizures are localized, and how seizures may propagate: namely, *dipolar modeling* much in the same way as in the case of epileptiform spikes; and *dynamical analysis of seizure development and propagation*. The expectation is that these methodological advances may contribute to an improvement of diagnostic methods.

A. Dipolar Modeling of Spikes at Seizure Onset

EEG signals recorded during seizures have been subject also to dipolar modeling, particularly of the spikes that tend to appear at seizure onset. Usually, these initial seizure spikes are more difficult to model than the transient interictal epileptiform spikes since they are more difficult to extract from background noise due to the contamination with movement and EMG artifacts. Gotman [36] made a comparative study of dipole models of epileptiform spikes and seizure onsets, recorded from the scalp and by means of intracerebral recordings. This allows a direct comparison what is, of course, much better than indirect comparisons where the results of dipole modeling are compared with the location of lesions identified in MRI scans. Nonetheless, we should realize that the sampling of the brain tissue by means of intracerebral electrodes is always very limited. Thus, if a dipole inverse solution is identified in a region where no intracerebral electrodes are located, the validation is left undecided. From Gotman's comparative study, we may draw the conclusion that dipole modeling is much less applicable in seizures, even only at the seizure onset, than to epileptiform spikes. Dipolar solutions may be identified that correspond to regions where there are intracerebral discharges, but the latter may not correspond to the onset of the seizure since the latter may be too focal to appear on the scalp EEG [36].

B. Decomposition of Seizure EEG Signals

Another approach consists in applying, first, a single-valued decomposition algorithm to decompose EEG seizure signals into a set of orthogonal spatio-temporal components (STCs) as proposed by Kobayashi *et al.* [54]. According to their description these authors recombine then these components to obtain new independent components with any arbitrary spatial distribution, and among the latter they select the distribution that correspond to dipoles having the largest amplitude. The latter is selected to represent the generator of the seizure at its onset. Appropriately, these authors call this approach the “*EEG through a software microscope*.” The method may appear similar to the MUSIC (multiple signal classification) method of Mosher *et al.* [84], but it differs from it because it does not define a noise component with a nonzero singular value as explained in mathematical terms in Kobayashi *et al.* [54].

There are other methods that have been also developed with the aim of performing spatio-temporal dipolar analysis of seizure EEG signals [19] and [103] using commercially available software (“BESA” and “FOCUS”). Kobayashi *et al.* [54] also applied these methods to their data but noted that the results were less consistent than those obtained using their “Software microscope,” since these other methods were not able to detect seizure activity that was not clearly apparent in scalp EEG.

Kobayashi *et al.* [54] applied the same method to EEG signals recorded during seizures of patients who had also intracranial electrodes for presurgical evaluation. They found that the source of seizure activity revealed by the “EEG software microscope” from the scalp recording corresponded with the source of seizure activity as estimated from the intracranial EEGs of the same patient, even if in the scalp EEG no seizure activity was evident at visual examination.

C. Measuring Seizure EEG Propagation: Linear and Nonlinear Methods

Although the question of how to localize the neuronal network generating epileptiform seizures is a matter of constant interest in clinical neurophysiology as indicated above, another feature of epileptic phenomena that is also very relevant is how to identify the *site of seizure onset* and the pattern of *seizure propagation* within the brain, given a set of intracranial EEG recordings. Also, in this case, analytical methods have contributed a lot. First, linear methods were used to estimate the degree of cross correlation (r^2), or of coherence as function of frequency, and the associated time delay between EEG signals recorded from several electrode sites, during presurgical exploration of the brain, particularly in cases of temporal lobe epilepsy, with the aim of determining the site of seizure onset and the propagation pattern of seizures in the brain. Pioneer work was done by Brazier [14] and further by Lieb [64] and Gotman [33]–[36]. These methods, however, have two limitations: one is that the estimation of a time delay from cross correlation or cross-spectral functions is not unambiguous, and the second is that these methods apply to linear relationship which, in general, do not hold in cases of EEG signals recorded during seizures. Therefore, new methods were developed that were not limited to linear relationships. One of these is the method of the average amount of mutual information (AAMI) introduced into the analysis of epileptiform activity by Mars and Lopes da Silva [73] and by Mars *et al.* [75], but this method is computationally rather heavy. Later, Pijn *et al.* [97], [99] introduced a method that allows a simpler estimation of association and time-delays between any two signals, regardless of whether or not their relationship is linear. This method consists in the computation of a nonlinear regression coefficient, called h^2 , by means of which the dependency of a signal on another is estimated [53]. If the relationship is linear, h^2 approximates the cross-correlation coefficient r^2 . This method was applied to EEG signals recorded during epileptiform seizures by Fernandes de Lima *et al.* [22] and by Pijn *et al.* [99]. The application of these quantitative analytical methods demonstrated that at the beginning of a seizure, considerable differences exist between r^2 and h^2 , indicating the presence of nonlinear relations between signals recorded from different sites, and that the propagation path of seizures may be detected if the very early part of the seizure is analyzed; later parts may show results that do not follow a clear pattern. The nonlinear analytical method h^2 , was applied to a study of seizure activity in a genetic model of absence seizures, the WAG/Rij rat, in order to find out whether these seizures were truly generalized, as classically assumed, or had a focal origin [77]. In this way, it was found that these seizures have a cortical origin in a well-defined part of the somato-sensory cortex, spreading very rapidly to other cortical areas and thalamus. This pattern, however, is only clearly detectable during the first 500 ms of the seizure since at later times the thalamo-cortical system behaves as an oscillator within which no clear leading and lagging areas can be distinguished. The h^2 method has also recently been shown to give reliable measures for estimating the degree and direction of functional coupling between neuronal populations in different types of human epilepsy [5], [111], [112], [118]. The computation of h^2 can give also indications about causality

with respect to whether signal x is caused by signal y (or *vice versa*), when h^2 is asymmetric, i.e., $h^2(x \rightarrow y)$ differs from $h^2(y \rightarrow x)$. With the same aim of estimating causality between EEG signals recorded from different areas Granger causality spectral analysis has been used successfully [16], [44].

IV. THE TRANSITION BETWEEN INTERICTAL AND SEIZURE ACTIVITY: DIFFERENT DYNAMICAL SCENARIO'S

A. Epilepsies as Dynamical Diseases

The question of whether it is possible to detect changes in the properties of EEG signals in the *period preceding an epileptic seizure* relative to the baseline interictal period, has been at the centre of attention for the last decade. In this respect, the expectations were that advanced EEG signal analysis would enable the detection of these changes and thus would make real the possibility of predicting the occurrence of seizures. This problem is not only of theoretical interest but it may have also practical implications. The main question thus is whether in the preictal period subtle changes in EEG signals may be detected using appropriate signal analytical methods. Of course, a preictal period exists always per definition; more important is to determine whether some EEG properties may characterize a *pro-ictal state*, i.e., a dynamical state of the neuronal networks that develops into an ictal state and that may be identified reliably on the basis of EEG signals. In order to analyze this question deeper, it is relevant to discuss the general theoretical framework of the dynamics of brain activity that may account *both* for normal and epileptic neuronal activities. Indeed it is well known that the brain of epileptic patients is not seizing all the time, except under the exceptional conditions of *status epilepticus*. This implies that even in the epileptic brain, some neuronal networks can display different kinds of dynamical states, or in other words they may have bi(multi) stable properties. The core of the question is to find out how the transition between two qualitatively and quantitatively different dynamical states, a “normal state” and an “epileptic state,” takes place.

In general terms and according to a theoretical framework that we have developed in recent years [69]–[71], epileptic disorders may be considered special cases of the large class of dynamical diseases, meaning those pathophysiologic states characterized by the occurrence of abnormal dynamics, a theoretical concept proposed by Glass and Mackey [31] that has been used in the context of epilepsy by us and others [3].

Observations both in experimental animal models and in human patients led us to consider that there are two basically different ways by which the transition of dynamical states in epileptic conditions can occur (Fig. 2):

- a) in the form of a “jump transition”;
- b) a gradual transition where a deformation of some crucial parameters of the neuronal networks takes place leading to the final dynamical state transition that becomes manifest as an epileptic seizure.

In the former case, one cannot identify a characteristic *pro-ictal* state, while in the latter this may be theoretical possible. The challenge for specialists in EEG signal analysis is whether this may also be realized in practice.

Two main classes of models that may explain the transition to epilepsy

Bifurcation dynamical model: jump transition – Case 1.

Deformation model: gradual transition – Case 2.

Fig. 2. Two main classes of models that may explain the dynamical transition from a normal brain state to an epileptic seizure. Above: the normal state is represented by the attractor on the left; the system can jump from this attractor to a “seizure attractor,” represented on the right, due to some input or intrinsic fluctuation; this is what may occur at the transition to an absence seizure; Below: the normal attractor shown on the left, can become deformed due to internal instabilities or to modulating influences from outside, or both, until it reaches the system the “seizure attractor” shown on the right. The state characterized by the intermediary attractor may be identifiable by specific properties of the corresponding EEG signals. This is what may occur in cases of mesial temporal lobe epilepsy.

This is the central question regarding automatic prediction of epileptic seizures.

B. The Road to Seizure Prediction

As Mormann *et al.* [83] appropriately stated the road to seizure prediction has been “long and winding,” from the early overreaching enthusiasm of the nineties, to the more subdued attitude of the present time. The early optimism rode on the crest of the wave of the popularity that the theory of complex nonlinear dynamical systems, in other words, “chaos theory” gained in this period. Thus, analytical methods based on these principles, such as the computation of the correlation dimension and the Lyapunov exponents, were introduced with the aim of detecting the transition that may anticipate an epileptic seizure. This is when Iasemidis *et al.* [48] proposed to compute the largest Lyapunov exponent of EEG signals recorded intracerebrally in epileptic patients as an indicator of an impending seizure and reported a decrease in chaoticity in the minutes before the seizure. Further Martinerie *et al.*, [76], and Elger and Lehnertz [20], [58] reported a preictal decrease in spatiotemporal complexity as measured by the correlation density. Thereafter the so-called “dynamical similarity index” was developed, which is a measure of the difference in dynamics between a preictal period and a reference window selected during a baseline period both in intracranial [61], [62] and even scalp EEG recordings [63]. With the same purpose several groups used related dynamical measures for distinguishing

EEG signals recorded in interictal and in preictal periods: the convergence of the largest Lyapunov exponents [49], the accumulated signal energy [66] and [30], phase synchronization [81, b] canonical discrimination analysis (Schiff *et al.* [104] and Osorio *et al.* [90] described an algorithm for rapid real-time detection and prediction of seizure clinical onset.

At the First International Collaborative Workshop on Seizure Prediction, several groups from different epilepsy centers applied their specific algorithms for seizure prediction to a common set of intracranial EEG signals including preictal and a seizure periods [57]. The main result was that no method convincingly demonstrated a satisfactory performance with respect to reliable seizure prediction. A general shortcoming was a lack of specificity regarding the identification of a preictal state. In addition, Harrison *et al.* [41] examined the sensitivity of the correlation integral and dimension for prediction of epileptic seizures comparing its performance against surrogate time series and concluded that neither the correlation dimension nor the correlation integral has predictive power for epileptic seizures. Further, they [42] reported that the accumulated energy, as a measure to predict seizures, did not appear to have predictive abilities for these data sets. Thus, estimates of sensitivity and specificity of the detection method are lacking in most of the earlier studies.

As stated by Mormann *et al.* [83] in their excellent critical review for seizure prediction algorithms to have practical value in clinical practice, it is necessary that these algorithms perform satisfactorily in unselected EEG data sets, with a performance that is better than that of a random prediction process. In order

to overcome the limitations of the pioneering studies, Aschenbrenner–Scheibe *et al.* [1] performed an analysis of the sensitivity and specificity of the correlation dimension method based on EEG signals of long duration recorded from 21 patients undergoing presurgical monitoring who carried indwelling electrodes. They tested namely whether a drop of the value of the correlation dimension several minutes before a seizure could be considered a reliable seizure predictor. They found that the mean length and amplitude of correlation dimension did not differ significantly between interictal and preictal signals.

An alternative stochastic approach of this same problem used a hidden Markov model; the model represents three states: interictal, preictal, and seizure states. It is assumed that transitions can occur not only sequentially between the three states in the order indicated above, but also that an increase in seizure probability can return back to the interictal state. This is not just a theoretical notion since in real situations one can encounter cases where an EEG pattern similar to that seen at the onset of a seizure may appear transiently, without a real seizure occurring. This stochastic model was used to test a novel seizure detection algorithm that appeared promising in predicting seizure onset [124].

C. Epileptic Seizures and Chaotic Dynamics: Any Relation?

The theoretical concepts according to the theory of complex dynamical systems that the transition of EEG signals from preictal to ictal phase represents the evolution of the neuronal system to a chaotic attractor, as initially proposed by Babloyantz and Destexhe [4], appeared to be an oversimplification. Indeed, comprehensive analyses using correlation dimension, tests for irreversibility and recurrence plots of EEG signals recorded intracranially both during interictal and ictal states in temporal lobe epilepsy patients showed that the EEG before and in the course of a seizure behaves as a nonstationary noisy signal during which both phases of low and high complexity may occur [96]. Further coarse-grained correlation dimension and coarse-grained correlation entropy were used for the nonlinear characterization of the EEG epochs and showed to discriminate well between EEG epochs recorded prior to and during seizures at locations displaying ictal activity [113]. Interestingly, signals recorded from the area of seizure onset display as a rule lower dimensions than signals recorded further away. Thus, the application of these mathematical tools provided some novel insights into the spatio-temporal dynamics of “epileptic brain states” [98] but was not of much practical use in helping to predict the occurrence of epileptic seizures in advance. Lai *et al.* [55] also noted that the use of Lyapunov exponents for seizure prediction presents difficulties due to the noisy character of the signals.

D. Are Active Methods of Probing Neuronal Excitability State Relevant Alternatives?

All the methods described above rely on an analysis of spontaneous EEG activity, what we may call *passive analysis*. Recently, an alternative approach was proposed based on an

active *paradigm*. This idea stems from the experimental observation that the MEG and EEG of patients in whom stroboscopic intermittent light stimulation (ILS) may elicit an epileptic seizure (photosensitive epilepsy), shows an enhancement of phase clustering particularly at higher harmonics (gamma frequency range) of the fundamental frequency of ILS during light stimulation. This is seen, however, only in those cases where ILS is followed by a seizure response, but not in cases where the latter does not occur. To quantify this phenomenon an index of phase clustering was derived [50]; this index is a quantitative measure of spectral phase demodulation; the most robust measure to discriminate between the MEG signals recorded during ILS in the periods preceding the onset of a seizure and in the periods that were not followed by a seizure, was found to be the relative phase clustering index (rPCI) that is the difference between the phase clustering index at high harmonics subtracted from that at the fundamental frequency of stimulation. This means that the value of the rPCI may eventually be used to anticipate the occurrence of the transition between a state characterized by a normal light driving response to an abnormal state consisting of paroxysmal oscillations [50], [92]. Recently, it was found that the responses evoked by ILS themselves, also appear to carry information about the state of enhanced excitability preceding the transition to the induced epileptic seizure [117]. This led us to ask the question whether also in other forms of epilepsy an *active stimulation paradigm* could be used to probe the state of excitability of neuronal networks, and thus identify possible changes that are likely to precede the transition to an epileptic seizure. The types of epileptic conditions that could easier be investigated in this respect were those cases of temporal lobe epilepsy, where patients carried chronically indwelling electrodes for presurgical evaluation. Of course, in these cases, one cannot use light or other kind of natural sensory stimulus. Thus, we resorted to use subthreshold electrical stimulation applied locally to the brain, by way of the indwelling electrodes, and to measure the relative phase clustering index (rPCI) of the local field potentials recorded during periods of electrical stimulation. Using this *active paradigm*, several electrode sites are stimulated in one patient, for example, by a 5 s long train of biphasic pulses (0.1 ms per phase) every 20 s, using a weak oscillating current (about 800 μA) at, for example, 20 Hz (for details see Kalitzin *et al.* [52]). High values of rPCI of the evoked field potentials, recorded during interictal periods, were associated with the most probable seizure onset sites (SOS). Most important, high values of rPCI from certain locations correlated with the time interval to the next seizure: in a series of six patients with temporal lobe epilepsy it was found that a value of rPCI > 0.6 indicated that a seizure would occur in less than 2 h, with an accuracy of more than 80% (Fig. 3). This finding can be seen as a “*proof-of-principle*” that the measurement of rPCI of short EEG epochs undergoing electrical stimulation, can be used for *probabilistic forecasting of an epileptic seizure*. Thus, we may conclude that although ictal transitions in many cases may be unpredictable, the assessment of the probability of some epileptic seizures occurring within a given time using an

rPCI as function of time preceding a seizure

Fig. 3. Illustration of the “seizure anticipation” features of the rPCI measurements. Above: plot of rPCI values (horizontal axis) versus the time to the next following seizure (vertical axis, hours) for each measurement. Below: pseudo-color and contour plot of the prediction error rates as a function of the rPCI threshold (vertical axis) and the prediction horizon (in hours, horizontal axis). Color scales indicates the error value; note that Values of rPCI > 0.6 indicate that there is a probability of > 80% of a seizure occurring within 2 h. (Adapted with permission from Kalitzin, Velis, Suffczynski, Parra, Lopes da Silva, *Clin. Neurophysiol.*, vol. 116, pp. 718–728, 2005).

active paradigm may be feasible. This method needs, however, to be tested using a wider population of patients in different environments.

V. MODELING AND CONTROLLING OF SEIZURES

A. The Need for Computational Neurosciences

Some of the methods presented and discussed above were inspired by the original papers on the possible relationships between brain activity and chaotic systems, a collection of a great part of which can be found in the book of the proceedings of the workshop “CHAOS IN BRAIN?” [59]. Whether or not this relationship may be relevant, it is certain that concepts derived from nonlinear dynamical theory have entered the field of what we may call *quantitative epileptology* to characterize the dynamical behavior of neuronal networks in the epileptic brain [69], [70], [71]. As stated by Lytton [74] in his recent review on “Computer modeling in epilepsy,” it has long been recognized that computer modeling will be required to “disentangle causality, to better understand seizure spread, and to understand and eventually predict treatment efficacy.” We may add that this is also required to advance scientifically in the field of signal processing with the aim of improving diagnostics and management of epileptic patients. Computational modeling can contribute greatly to get insight into the mechanisms underlying seizure generation. The latter have to be seen as phenomena at the level of populations of neurons in the context of their dynamical properties. In this way,

specific computational models of epileptogenic neuronal networks were constructed and are being used to test novel methods of analysis.

As mentioned already, we should distinguish two basically different processes by which the transition of dynamical state from a normal state to the seizure state may occur:

- the “jump transition,” that is unpredictable;
- the “gradual change in parameter set,” that may be detectable if the appropriate analytical method is applied.

1) *The Case of “Jump Transitions”*: Based on an earlier computational model of interacting neuronal thalamo-cortical networks [106], the conditions under which these networks generate epileptiform activity in the form of spike and wave (SW) discharges were investigated [107]. The model was constructed at the macroscopic level since such approach allows investigating dynamical properties of the system and the role played by different mechanisms in the process of seizure generation, both at short- and long-time scales. The main results were that (i) SW discharges represent dynamical bifurcations that occur in a bistable neuronal network and that (ii) the durations of paroxysmal and normal epochs have exponential distributions, indicating that transitions between these two stable states occur randomly over time with constant probabilities. This prediction was tested experimentally in genetic rat models of absence epilepsies and in cases of human absences [108]. It was found that in certain cases, but not in all, the transitions between ictal and interictal states can be modeled by a Poisson process operating in a bistable network. Further, the experimental test revealed

also that the dynamics of ictal epochs differ from those of interictal states, and that seizure initiation can be accounted for by a random walk process while seizure termination is often mediated by deterministic mechanisms. Another prediction of the model is that an ictal state may be aborted by a single counter stimulus.

The assumption that in some cases the transitions between ictal and interictal states can be modeled by a Poisson process operating in a bistable network was confirmed by the experimental tests. This implies that the occurrence of this kind of absence seizures cannot be predicted. It is important to note, however, that this conclusion cannot be generalized to other types of seizure conditions without further analysis, as discussed below. This conclusion underscores the notion that different kinds of epileptic conditions can have different mechanisms, what is also supported by neurobiological observations.

2) *The "Case of Gradual Changes in Parameter Set"*: The role of this mechanism in the generation of epileptic seizures can be clearly demonstrated by the simulations performed using the computational model of the hippocampal formation constructed by Wendling *et al.* [119], [120] to account for the occurrence of epileptic seizures in patients with mesial temporal lobe epilepsy (MTLE). The model consists of four lumps of neuronal populations, namely, pyramidal neurons, excitatory interneurons, and two kinds of inhibitory interneurons: one that is responsible for inhibitory currents with fast kinetics at the level of somatic synapses on pyramidal neurons, and the other for inhibitory currents with slow kinetics at the level of the dendrites. Further, the model includes the important property that the latter interneurons also inhibit the former, as shown by Banks *et al.* [8]. Using this model, the hypothesis that a basic mechanism underlying epileptogenicity in the kainite rat model of the hippocampus is a decrease of slow dendritic inhibition and a subsequent increase of fast somatic inhibition, as proposed by Cossart *et al.* [18] was successfully tested. Indeed using the model, these changes in inhibitory synaptic gains were shown to be responsible for the change of neuronal activity reflected in the field potential in the form of sustained spiking at first, and low-voltage high-frequency oscillations later, culminating in the emergence of typical seizure activity. These computer simulations underscore the hypothesis that this form of epileptic seizures are caused by a gradual change in some parameters that are crucial for the control of the dynamical state of underlying neuronal network activity. Currently, the same model is being investigated further in the sense of attempting to solve an inverse problem, i.e., to identify the set of model's parameters based on observed EEG signals recorded at different stages, interictal, preictal, at seizure onset and during a seizure [24].

VI. CONCLUDING REMARKS

The computational models described above are based on the assumption that in the epileptic brain, some neuronal networks can display different kinds of dynamical states because they possess an abnormal set of control parameters. In other words, they may have bi(multi) stable properties. This means that in addition to a normal steady state they also have an abnormal one characterized by widespread synchronous activity (the seizure) and that the transition between these two states may occur more or

less abruptly. This accounts for the two main characteristics of epilepsy: 1) that an epileptic brain can function apparently normally between seizures (i.e., during the interictal state) and 2) that the seizures occur in a paroxysmal way, thereby impairing brain functioning to a lesser or greater extent. In this sense, epileptic disorders may be considered special cases of the large class of dynamical diseases. The theory of nonlinear dynamics offers the possibility to understand, in formal terms, how the occurrence of dynamical diseases, such as epilepsy, takes place.

To answer the question of how the initiation of epileptic seizures takes place implies the development of algorithms that are capable of detecting such an initiation in a reliable way. Most challenging is the question whether analytical methods can forecast an impending seizure and, whether this methodology may be coupled with closed-loop interventions aiming at avoiding the occurrence or the propagation of seizures. The current trend is to develop analytical methods, some of which are already being tested in clinical practice, in order to solve the problem of "forecasting seizures," and to perform statistical validation tests of seizure-forecasting algorithms.

A bottleneck with respect to the development of such methods is the fact that one still lacks general models of seizure initiation. Some progress has been made recently in the field of computer modeling of these phenomena, and the notion that different types of epileptic seizures can occur according to different dynamical scenarios is becoming generally accepted. In this context, it is important to build up links between the computational model dynamics and the analytical algorithms that are proposed for forecasting epileptic seizures.

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