Intelligent implantable medical devices: the epilepsy problem

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ABSTRACT

In this paper we present our work analysing electroencephalographic (EEG) signals for the detection of seizure precursors in epilepsy. Volterra-systems and Cellular Nonlinear Networks are considered for a multidimensional signal analysis which is called the feature extraction problem throughout this contribution. Recent results obtained by applying a pattern detection algorithm and a nonlinear prediction of brain electrical activity will be discussed in detail. The aim of this interdisciplinary project is the realization of an implantable seizure warning and preventing system.

Keywords: epilepsy, nonlinear signal analysis, precursor detection, Volterra-systems, Cellular Nonlinear Networks, seizure warning

1. INTRODUCTION

The realization of intelligent medical devices is of rapidly increasing importance for a successful treatment of patients. Although, great efforts have been made in a lot of interdisciplinary investigations leading e.g. to improved non-invasive blood testing devices [18, 19], symptom-based disease diagnosis systems, cochlea implants and neurostimulators, the development of an implantable brain controlling system with stored programmability remains unsolved up to now. Naturally, necessary requirements are very often miniaturization, a low-power realization technique and the capability of supercomputer to allow a real-time multidimensional signal processing with complex algorithms. Electronic devices based on Cellular Nonlinear Networks which own these characteristics have approximately a size of $1cm^2$. A Cellular Nonlinear Networks Universal Machine [20] is a tera (10^{12}) instructions per second brain-like supercomputer on a chip with stored programmability. Considering a chip realization of these networks as a possible intelligent implantable medical device for a brain the real challenge is the determination of the cell coupling structure and the derivation of the neural algorithm to solve a certain problem. In this paper the detection of precursors of epileptic seizures by Cellular Nonlinear Networks is treated

Worldwide approximately 1 % of the population suffer from a recurrent malfunction of the brain termed epileptic seizure. Because of the sudden occurrence of seizures, which characterize the disease epilepsy, very often a high risk of injury has to be taken into account. Presently, regarding e.g. 200 000 affected individuals in the Federal Republic of Germany there is no applicable therapy for about 25 % of all patients, i.e. a satisfactorily seizure control by antiepileptic drugs or in an epilepsy surgery the removal of the focal area of the brain from where the seizures originate. Since EEG signals represent the electrical activity of populations of neurons, a multidimensional signal analysis in a preseizure state may uncover brain dynamics finally leading to the onset of an epileptic seizure [21, 22]. The main problem, which has been treated in a lot of interdisciplinary investigations, is the determination signal features reliably allowing seizure precursor detection. Although, seemingly the application of recently introduced nonlinear analysis procedures [2-5] provides information predictive of an impending seizure in several cases, the so-called feature extraction problem is still an exciting challenge.

Cellular Nonlinear Networks and Volterra systems are considered for the feature extraction problem in epilepsy in this overview of our work. While the above mentioned systems are introduced in section 2, different feature extraction algorithms the so-called pattern detection algorithm and procedures for a prediction of EEG signals are presented in section 3. While these networks have been used for a prediction and pattern detection, first results for a signal predic-

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tion have been obtained with Volterra systems. A detailed discussion of all results will be given in section 4 and finally a conclusion in section 5.

2. VOLTERRA SYSTEMS AND CELLULAR NONLINEAR NETWORKS

2.1 Volterra systems (VS)

By analysing a nonlinear RLC circuit VS have been considered for the first time by Wiener [13] who developed in his famous work a comprehensive theory [15], the so-called Wiener theory of nonlinear systems. VS are defined by n-linear time-invariant operations based on functionals which have been introduced by the Italian mathematician Vito Volterra [14] studying certain integral and integro-differential equations. Although, a broad class of nonlinear systems could be identified by VS [23] usually weakly nonlinear cases are treated because of a considerable calculation complexity for strong nonlinearities. In this contribution time-discrete k-th order VS are considered represented by

$$y(t_n) = \sum_{m=1}^{k} y_m(t_n) = \sum_{m=1}^{k} H_m[x(t_n)] \tag{1}$$

with

$$y_m(t_n) = \sum_{\tau_1}^{\infty} \cdots \sum_{\tau_m}^{\infty} h_m(\tau_1, \ldots, \tau_m) x(t_{n-\tau_1}) \cdots x(t_{n-\tau_m}). \tag{2}$$

As shown in Fig.1 $y(t_n)$ is the system output to a excitation $x(t_n)$ and $h_m(\tau_1,\ldots,\tau_m)$ denotes the Volterra kernel of the homogeneous system $H_m[x(t_n)]$. Especially, we assume in the following causal and BIBO stable sytems.

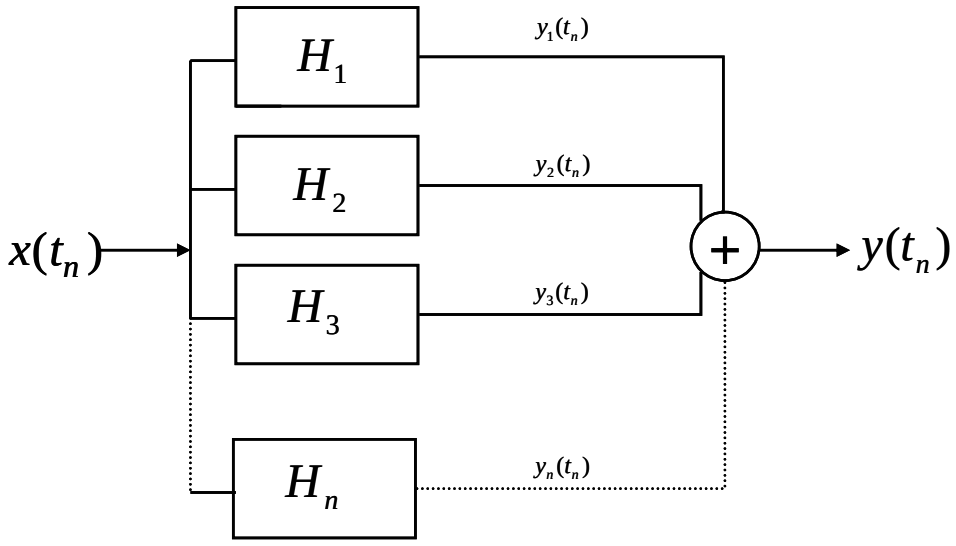


Fig. 1 n-th order Volterra system

Different algorithms allowing an precise determination of Volterra kernels have been proposed and studied in several investigations [24]. While Schetzen calculated the m-th order impulse response and introduced a higher order cross correlation method, an algorithm for homogeneous systems [25-27] based on the determination of higher order cross spectra has been generalized by Koukoulas [12] to non-causal non-homogeneous VS. Unfortunately these methods are based on stationary Gaussian input processes. As shown in [11] Eqn. 1 can be transformed into a normal equation allowing a calculation of Volterra kernels through a matrix inversion. In our investigations we followed this way and applied a RLS algorithm [2] in all cases.

2.2 Cellular Nonlinear Networks (CNN)

Since CNN have been introduced 1988 by Chua and Yang [28] these networks became a paradigm for nonlinear information processing. According to a later given generalized definition [1] consists a CNN of spatially discrete nonlinear dynamical systems which are coupled within a prescribed sphere of influence to all neighbouring systems called cells. While by applying the pattern detection algorithm the so-called Chua-Yang model represented by the system

$$\dot{x}_i(t) = -x_i(t) + \sum_{j \in S_i(r)} a_j \cdot y_j(t) + b_j \cdot u_j + z, \quad a_j, b_j, \text{ and } z \in \Re \tag{3}$$

of locally coupled nonlinear differential equations is used, we consider for the prediction problem autonomous multilayer discrete-time networks (DTCNN) with state equations of the form

$$x_i^l(t_{n+1}) = -x_i^l(t_n) + \sum_{l'=1}^{L} \sum_{\tau=0}^{T} \sum_{j \in S_i(r)} a_j^{\tau l' l}\left[x_j^{l'}(t_{n-\tau})\right]. \tag{4}$$

$x_i^l(t_{n+1})$ denotes the state of the i-th cell C_i in layer l at time t_{n+1}, $S_i(r)$ is the sphere of influence of a cell with radius r and $a_j^{\tau l' l}\left[x_j^{l'}(t_{n-\tau})\right]$ represent translation invariant delay-type polynomial feedback functions given by

$$a_j^{\tau l' l}\left[x_j^{l'}(t_{n-\tau})\right] = \sum_{k=1}^{K} a_j^{k \tau l' l} \cdot \left(y_j^{l'}(t_{n-\tau})\right)^k . \tag{5}$$

The well known nonlinear function

$$y_j(t) = f\left(x_j(t)\right) = \frac{1}{2}\left(\left|x_j(t)+1\right| - \left|x_j(t)-1\right|\right)$$

is taken for continuous time networks with cell output activity $y_j(t)$ whereas $y_j^{l'}(t_n) = f\left(x_j^{l'}(t_n)\right) = x_j^{l'}(t_n)$ is assumed without loss of generality for DTCNN throughout this contribution.

3. FEATURE EXTRACTION

The most challenging problem for the realization of an implantable system simply giving a warning before the onset of an epileptic seizure is the derivation of appropriate feature extraction methods allowing reliable precursor detection with high sensitivity and specificity [6]. In comparison to a classical analysis of EEG signals which has been performed in several investigations [29] e.g. by using spectral analysis procedures or by calculating autoregressive moving average models, recently introduced nonlinear EEG analysis methods clearly contributing to the precursor detection problem. Lehnertz [21] showed that values of an effective correlation dimension were decreased prior to seizure onset. Furthermore,

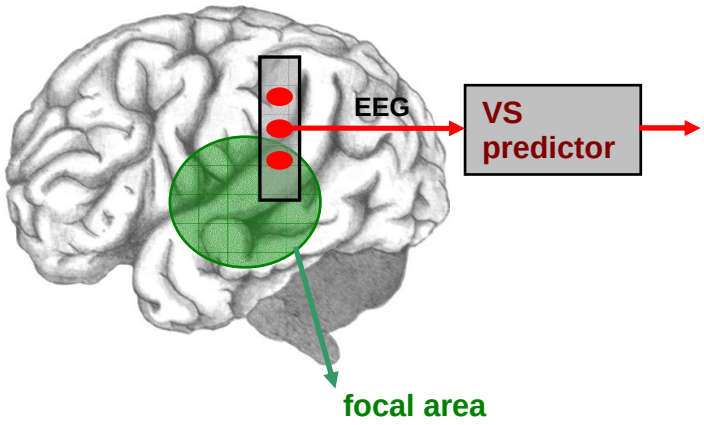
Sowa [8] used CNN to estimate the phase synchronization between time series obtained from different recording channels and observed a long-lasting drop of synchronization before a seizure as compared to values in a seizure-free period. In earlier studies [9] we have derived a CNN algorithm allowing an approximation of the above mentioned effective correlation dimension with a high accuracy. Furthermore, we proposed procedures for a prediction of EEG signals by VS [2] and DTCNN [3] and presented a pattern detection algorithm [4] by using a Chua-Yang model of a CNN. Finally, in first investigations [10] we consider reaction-diffusion CNN for a modelling approach. While the prediction of EEG signals and the pattern detection algorithm is discussed in this overview, the results obtained for reaction-diffusion CNN are given in a further paper.

3.1 Prediction of EEG signals

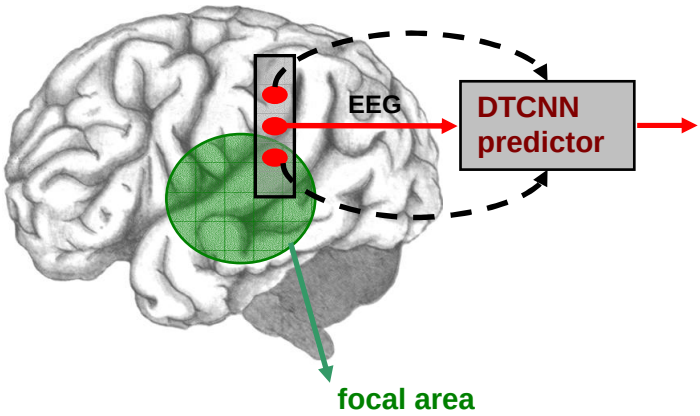
VS and DTCNN have been considered for a prediction of EEG signals using different recordings of brain electrical activity of 6 patients obtained in invasive multi-electrode presurgical evaluations [30]. A detailed description of the used data base is given in section 4. By minimizing a quadratic error measure in all cases a nonlinear predictor has been determined for each data segment of an EEG recording. Following this way we obtain a time-sequence of predictor parameter for each recording which has to be analyzed with regard to distinct changes before the onset of an epileptic seizure. While in a signal prediction with VS according to

$$x(t_n) = \sum_{m=1}^{k} \sum_{\tau_1} \cdots \sum_{\tau_m} h_m(\tau_1, \ldots, \tau_m) x(t_{n-\tau_1}) \cdots x(t_{n-\tau_m}) \tag{6}$$

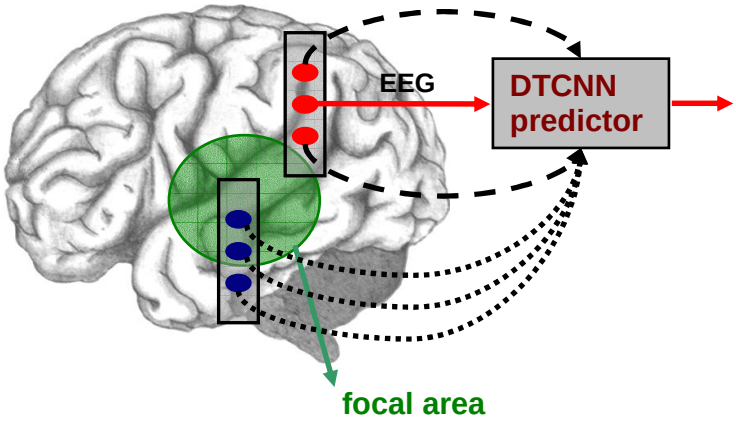
only previous values $x(t_{n-1}), \ldots, x(t_{n-m})$ of same electrode will be taken estimating $x(t_n)$ also values of neighbouring electrodes or electrode arrays are taken by using the above mentioned single or multilayer DTCNN, the prediction scheme is shown in Fig. 2.



Fig, 2a Prediction scheme for EEG signals using VS. AD conversion and pre-processing steps are not shown for the sake of convenience



Fig, 2b Prediction scheme for EEG signals using single layer DTCNN whereas signal values (dashed line) of neighbouring electrodes will be considered in the signal prediction. AD conversion and pre-processing steps are not shown for the sake of convenience



Fig, 2c Prediction scheme for EEG signals using multilayer DTCNN whereas signal values (dashed line) of neighbouring electrodes and of different electrode arrays (dotted line) will be considered in the signal prediction. AD conversion and pre-processing steps are not shown for the sake of convenience

In order to analyse the nonlinear strength of the obtained VS and DTCNN predictor for successive data segments the so-called nonlinear strength

$$d_{VS}(m) = \frac{\sum_{n>1} \sum_{\tau_1,\ldots,\tau_n} \left| h_{n,m}(\tau_1,\ldots,\tau_n) \right|}{\sum_{\tau_1} \left| h_{1,m}(\tau_1) \right|} \tag{7}$$

has been calculated for VS where $h_{n,m}(\tau_1,\ldots,\tau_n)$ denotes the n-th order Volterra kernel of the m-th data segment. Similarly

$$\psi_{DTCNN}(m,l,l') = \frac{\sum_j \sum_{k>1} \sum_\tau \left| a_j^{k\tau l' l} \right|}{\sum_j \sum_\tau \left| a_j^{1\tau l' l} \right|} \tag{8}$$

was considered in the analysis of single and multilayer DTCNN in all cases.

3.2 Pattern detection by CNN

In the pattern detection algorithm (PDP) a statistical analysis of EEG signals will be performed in a way similar to a classical level crossing analysis of stochastic processes [31-33], it should be noted that not a detection of certain signal pattern will be treated. Assuming that the signal of a data segment m could be regarded as the realization of an almost stationary random process ξ_m (t) then as shown in Fig. 3 the joint probability will be determined that ξ_m (t) is below or above a given level R at times t_i, i=1,…,n.

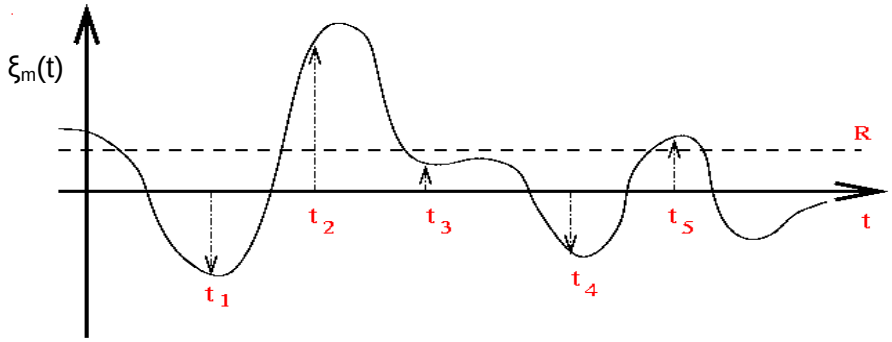


Fig. 3 Event of the pattern detection algorithm. While ξ_m (t) is below a certain level R at t_1, t_3 and t_5 it is above R at t_2 and t_4.

In this paper the occurrence frequency of above mentioned events will be estimated and distinct changes of it detected for successive data segments by using Chua-Yang CNN. Therefore normalized data segments with zero mean have been binarized for different level values R, an example is given Fig.4.

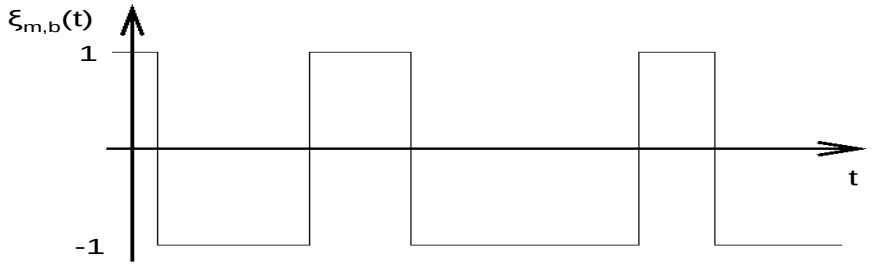


Fig.4 Normalized binary valued EEG signal $\xi_{m,b}(t)$ with zero mean vs. t

Then, as shown in Fig. 5, data segments of $\xi_{m,b}(t)$ are stored linewise as inputs on two-dimensional CNN leading to an image with binary pattern. Throughout this contribution we consider pattern with 3x3 pixels, i.e. we study the

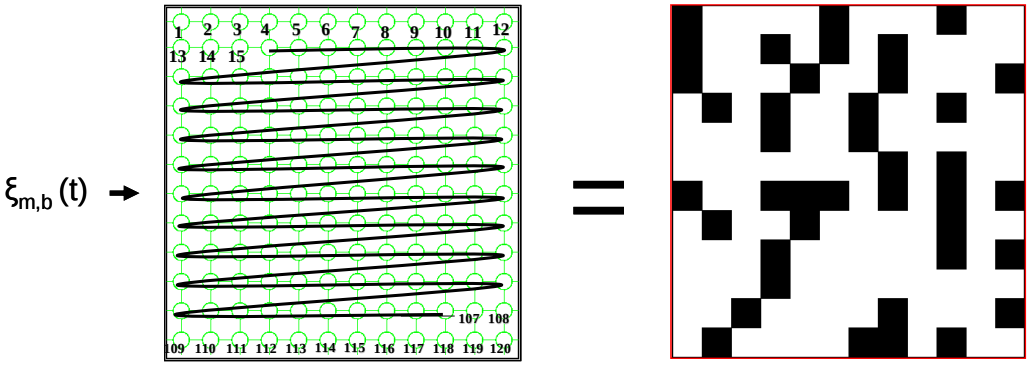


Fig. 5 EEG data segment stored as input on a two-dimensional CNN leading to an image with binary pattern

occurrence of events by CNN defined at $t_1,\ldots,t_9$ allowing the application of the well-known pattern detection template [36] on existing CNN based electronic devices [34, 35]. In this way event counting or event detection is performed through pattern counting or pattern detection on a CNN. Obviously, for 3x3 pixels there are altogether 2^9=512 different pattern possibly repeated occurring within a data segment, i.e. in order to adapt the PDP to a patient the probability concerning all 512 pattern has to be analysed in a pre-processing evaluation for successive segments with regard to distinct changes before the seizure onset. By using a programmable device the obtained results may lead e.g. to an application of the PDP on a patient detecting changes of a certain pattern occurrence as a possible precursor of an impending seizure.

By focusing on those patterns having a single occurrence in a data segment a generalized form of the PDP has been applied to EEG recordings of all patients of our database in recent investigations [4] and in the framework of this paper. Thereby, also the joint probability concerning EEG signals of different electrodes will be studied in a so-called Pattern Occurrence Image (POI), i.e. a seizure warning follows if a pattern jointly occurs m times in n segments in order to render the generalized definition more precisely. An example is given in Fig. 6.

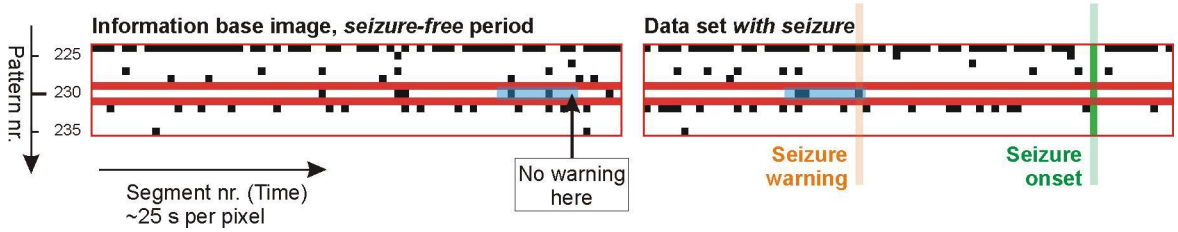


Fig. 6 Example of a POI allowing the analysis of brain electrical activity through a time window, shifted over the result of the PDP. The windowing operation is followed by a thresholding. In each line of the image the occurrence of one pattern encoded by black pixels is shown for successive data segments. In this case a seizure warning is follows when the window covers more than 2 pattern occurrences.

4. RESULTS

4.1 Database

The results presented in this contribution are obtained for several invasive recordings of the electrocorticogram (ECoG) or the stereo-EEG (SEEG) via implanted electrodes from 6 different patients. An implantation scheme is given in Fig. 7 as an example. The recording of bio-electrical activity in different anatomical regions of a brain has been performed in the Clinic of Epileptology of the University of Bonn in the framework of presurgical evaluations.

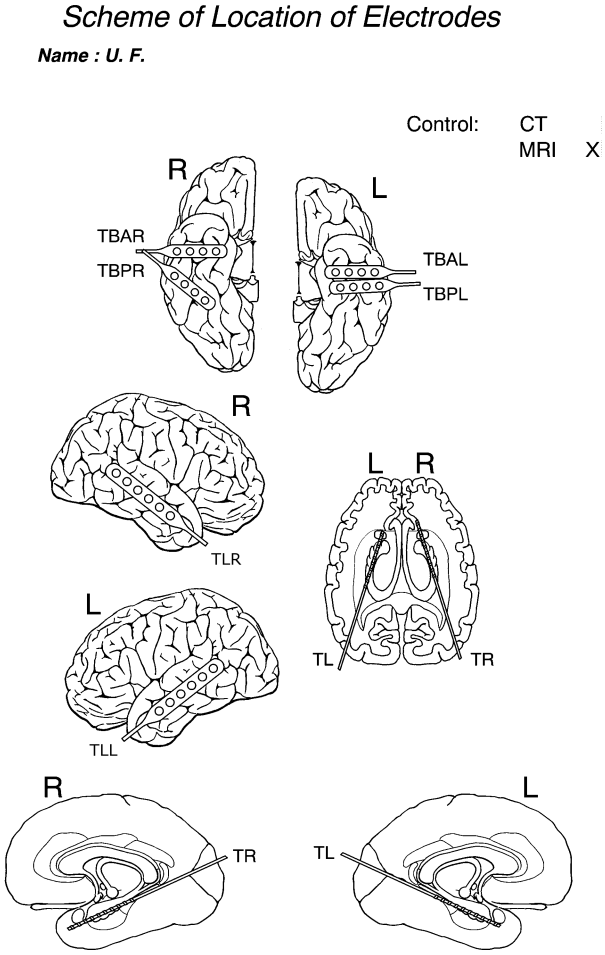


Fig. 7 Example of an implantation scheme

Multi-channel short term recordings as well as long-lasting recordings of EEG signals have been considered in our studies. The data base comprises short term recordings of 5 different patients including 11 clinical seizures and duration not longer than about 30 to 90 minutes. In all cases non-overlapping data segments with 5192 and 7200 values have been processed equivalent to a period of 30 seconds at sampling rates of 173 Hz and 260 Hz. Furthermore long-lasting recordings have been analyzed in our studies. In this paper results are given for a patient whose data consists of 16 successive recordings of EEG signals altogether covering a period of 6 days. This data were obtained at a sampling rate of 200 Hz resulting in segment lengths of 6000 values (30 seconds) and 3000 values (15 seconds). No pre-processing has been applied to the EEG time series.

4.2 Prediction of EEG signals by means of VS

In a first study a nonlinear prediction of EEG time series with zero mean - normalized to a range $1 \geq x(t_n) \geq -1$ - has been performed by VS using all short term recordings of 4 different patients. Thereby, in nearly all cases Volterra kernels of third order systems as defined in Eqn. 6 have been determined by applying a RLS [11] based algorithm with reduced calculation complexity. Regarding our results, an accurate prediction of EEG signals by VS has been obtained throughout our investigations. Exemplarily, a typical result is given in Fig. 8. In order to minimize the mean square error

$$\varepsilon = \sum_n e^2(t_n) = \sum_n \left(x(t_n) - x_{VS}(t_n)\right)^2 \tag{9}$$

for a certain data segment, the coefficients of the Volterra kernels were determined in this case by using the Variable Metric Method [37]. Here, $x_{VS}(t_n)$ denotes the prediction result and $x(t_n)$ represents a corresponding value of the EEG time series.

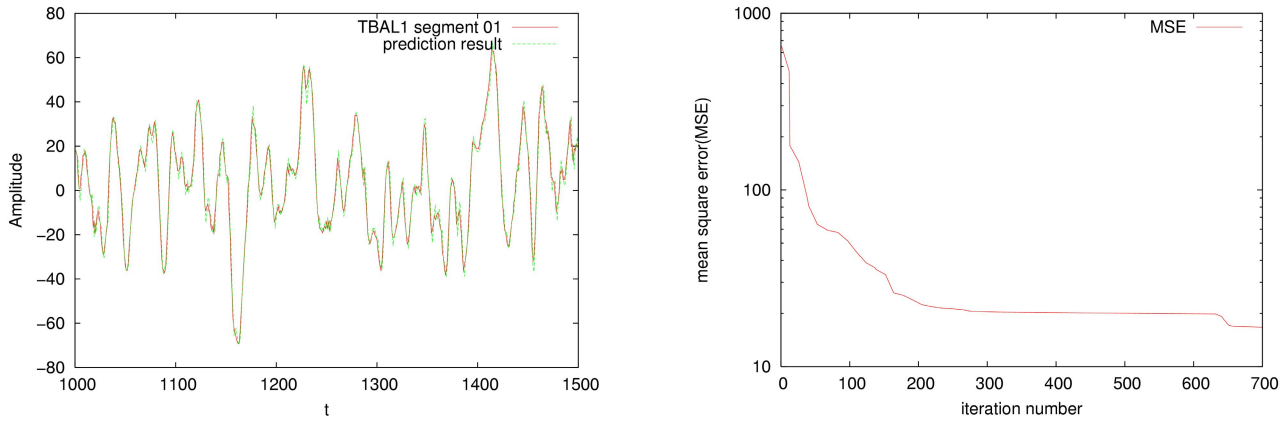


Fig. 8: **Left**: Prediction result vs. time obtained for electrode TBAL1 **Right:** Mean square error vs. iteration number

In this case, the predictor has been determined for the first data segment of the electrode TBAL1.

Furthermore, the obtained sequence of prediction coefficients was analyzed in detail by calculating $d_{VS}(m)$ for each data segment of all EEG recordings. In Fig. 9 results obtained from 4 different patients (a-d) are shown, giving the feature $d_{VS}(m)$ versus interval number m. In all treated cases a drop in the mean value $d_{VS}(m)$ can be observed before the onset of a seizure, which possibly points to the occurrence of a seizure precursor. This behaviour can be seen only before and during an epileptic seizure. Although, these observations indicate distinct changes of the nonlinear strength $d_{VS}(m)$ as compared to seizure free periods of EEG activity. These results have to be verified for long-lasting multi-channel recordings what will be treated in further investigations.

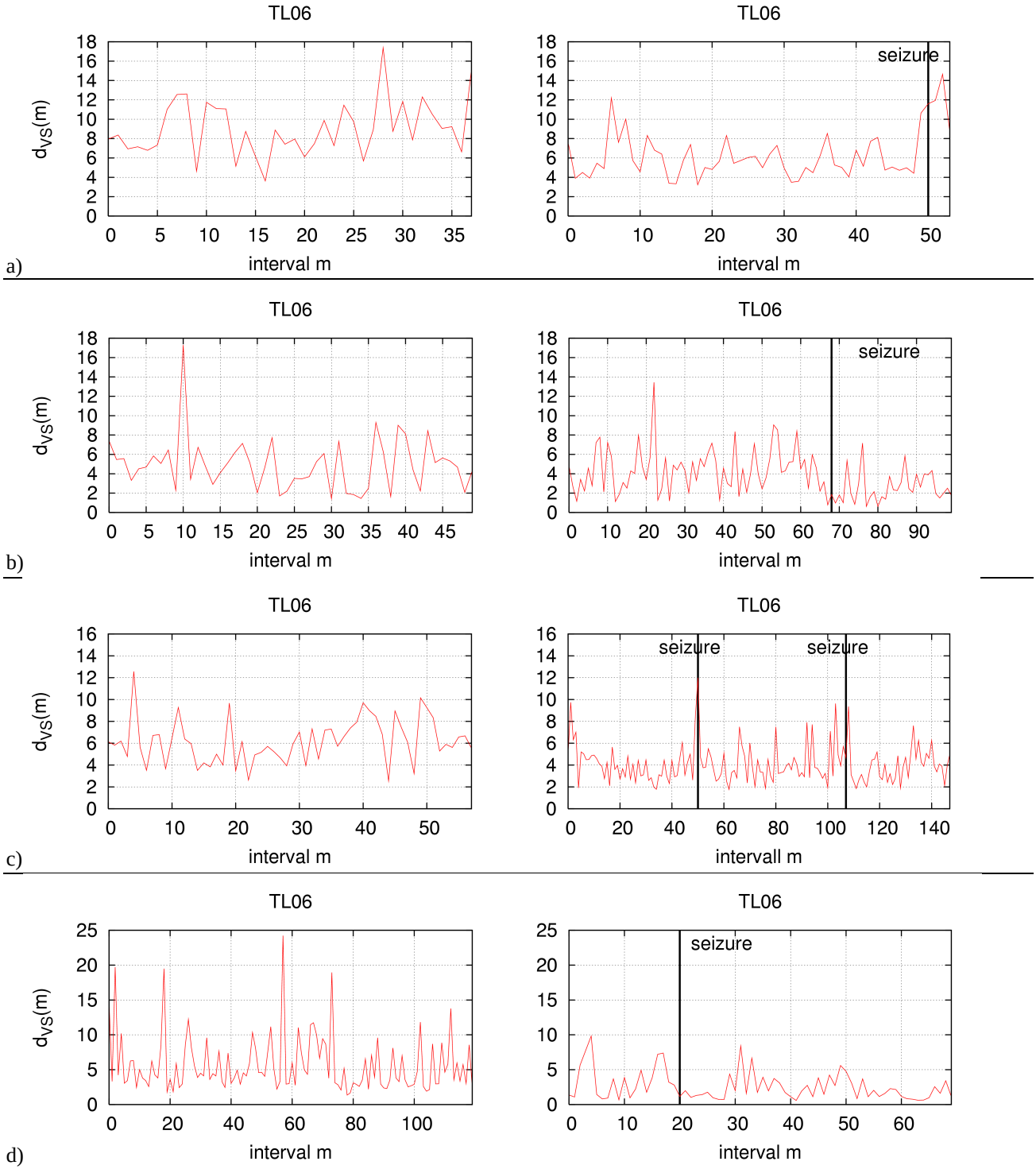


Fig. 9: d_{VS}(m) vs. segment number m. The results were obtained by using the bio-electrical activity of the depth electrode TL06 of 4 different patients (a-d). **Left :** intervals without seizure **Right :** intervals with seizure

4.3 Prediction of EEG signals by means of DTCNN

The results given in the following are based on the long-lasting recording of one patient by using a DTCNN with 3 x 1 cells and 3rd order polynomial weight functions including a delayed feedback function for T=1. While the analysis of single layer networks has been discussed in a previous paper [7] a two layer autonomous DTCNN has been applied throughout this analysis. Therefore, 8 different templates have to be determined for each data segment in a supervised optimization procedure. During this process the relative MSE according to

$$e(m) = \sum_{l} \sum_{n} \sum_{i} \frac{\left(x_i^l(t_n) - \hat{x}_i^l(t_n)\right)^2}{x_i^{l^2}(t_n)} \tag{11}$$

has been minimized yielding a typical minimum of about 7 %. An example is shown in Fig. 10.

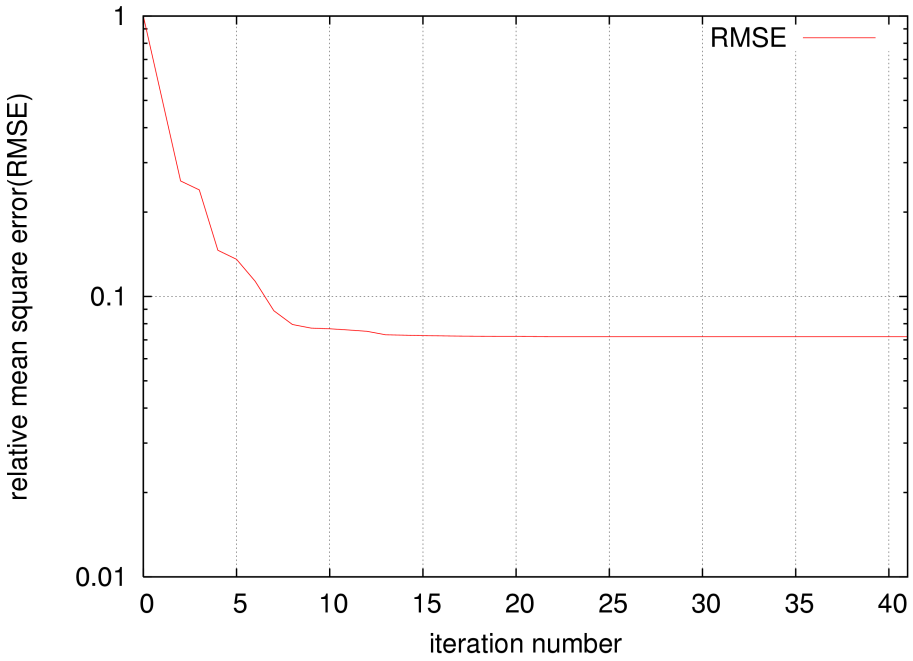


Fig. 10: RMSE vs. iteration number by using the BFGS optimization method.

In the foregoing studies based on VS time series with zero mean - normalized to a range $1 \geq x(t_n) \geq -1$ - have been analyzed by applying a BFGS [37] optimization method in order to minimize e(m) for successive data segments. Here, a typical calculation time of about 5 to 10 minutes on a 2 Ghz Celeron CPU has been necessary for each data segment in the simulation experiments.

Fig. 11a and 11b show the features $\psi_{DTCNN}(m,1,1)$ and $\psi_{DTCNN}(m,2,2)$ as functions of the segment number m. Here EEG time series of the depth electrode array TL have been fed to the first layer of the considered DTCNN and those of the array TBAL have been fed to the second layer of the network. Obviously, there appears a distinct increase of both features before the seizure onsets, i.e. an increasing nonlinearity of the predictor networks occurs before a seizure. At the onset there is a drop indicating that already a linear prediction leads to accurate results during an epileptic seizure.

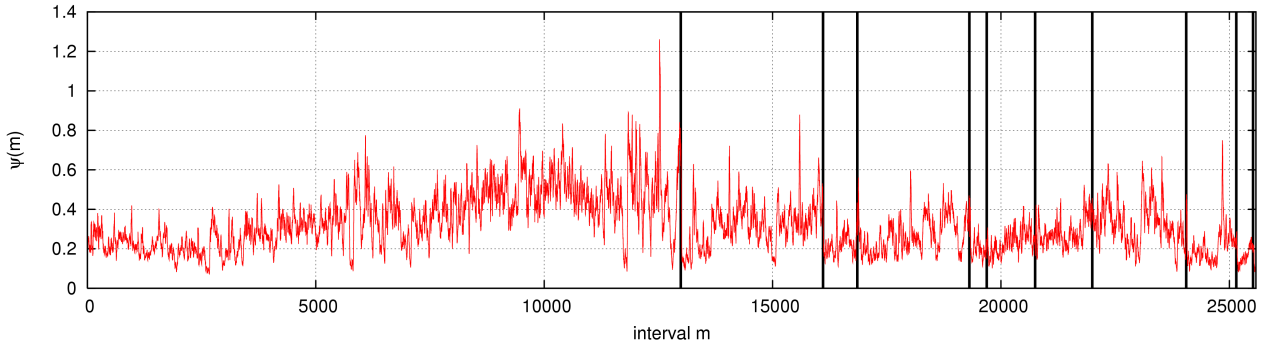


Fig. 11a $\psi_{DTCNN}(m,1,1)$ vs. segment number m.

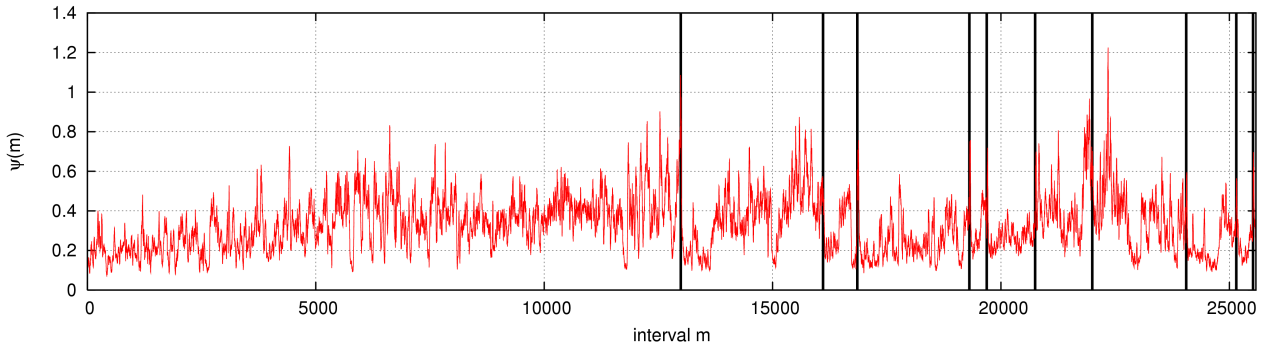


Fig. 11b $\psi_{DTCNN}(m,2,2)$ vs. segment number m.

In Fig. 12a and 12b where the second layer has been fed from the brain electrical activity of the array TLL further results of $\psi_{DTCNN}(m,1,1)$ and $\psi_{DTCNN}(m,2,2)$ are given. In principle the same kind of results can be observed as for the first given electrode configuration: a drop at the seizure onsets occur after an increase of both features.

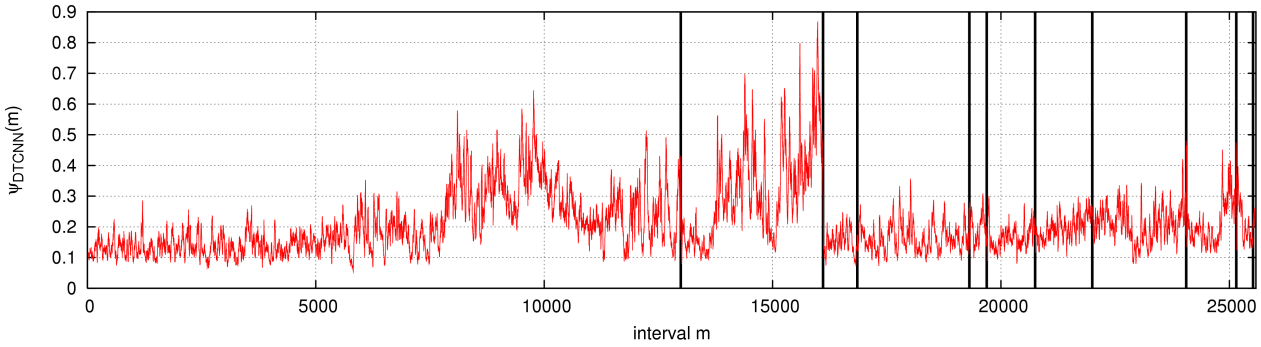


Fig. 12a $\psi_{DTCNN}(m,1,1)$ vs. segment number m.

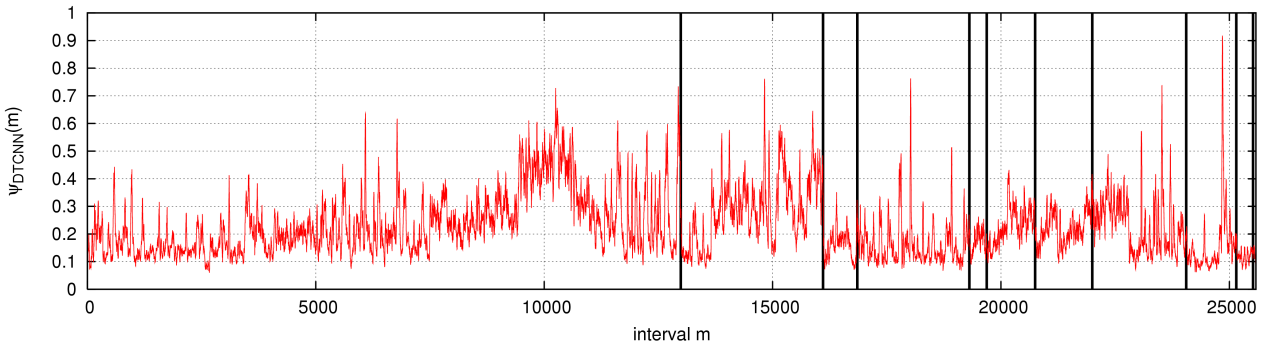


Fig. 12b $\psi_{DTCNN}(m,2,2)$ vs. segment number m.

Therefore comparing the results obtained for the different electrode array configurations a similar shape of the features can be noticed. Apparently an increase of the predictor nonlinearity before the first seizure onset starts earlier concerning the first configuration. This may be due to the interaction to the second layer which represents different electrode arrays treated. Although remarkable changes of $\psi_{DTCNN}(m,l,l')$ can be observed for both electrode configurations, these results must be verified for long-lasting recordings of other patients and will be treated in further studies

4.4 Pattern Detection Algorithm

Although, the PDP has been applied to all recordings of the above mentioned data base, only results obtained from a long-lasting recording are discussed in the following. The joint occurrence behaviour of the chosen pattern of up to five electrodes was studied in order to find a distinct change before the seizure onset. In Fig. 13 the results of a POI analysis for three different electrodes are given.

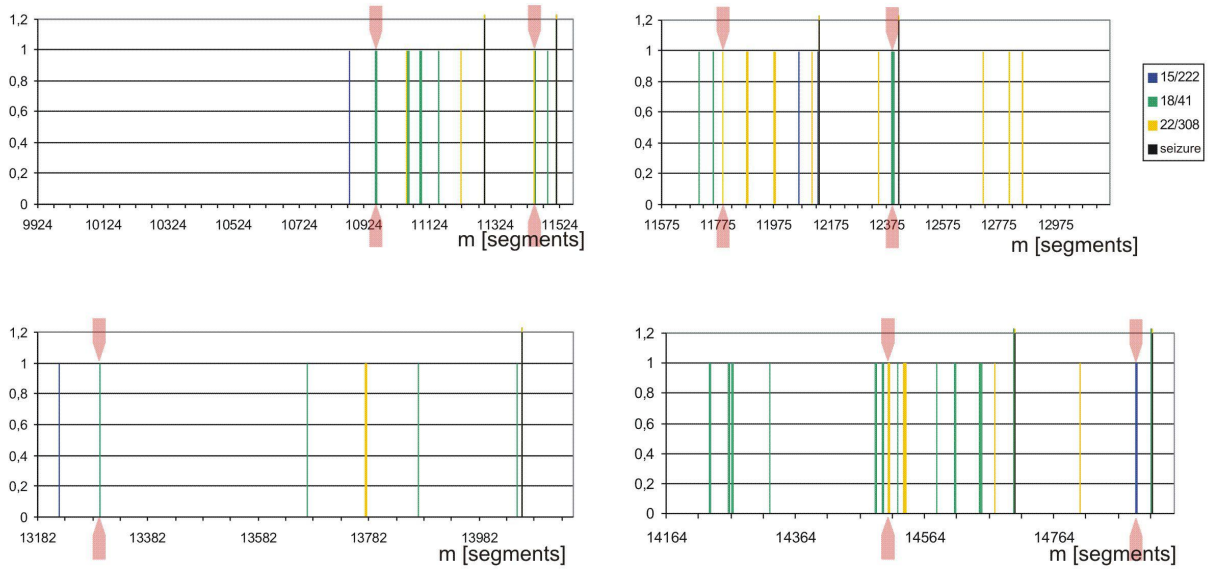
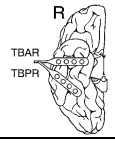
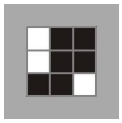
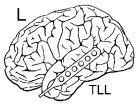
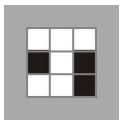
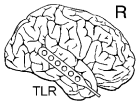
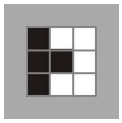


Fig. 13 : Results of the Pattern Detection Algorithm (PDP) based on three observed electrode points. Seizures are marked by black vertical lines, seizure warnings are marked by grey arrows. A seizure warning is given before the onset, when a POI-event has occurred in at least two of the three studied electrodes.

Therefore, our investigations show that a seizure warning may be possible if two of three different patterns occur at least five times in a time window of 6 data segments. The patterns and corresponding electrodes for this case are given in Table 1.

Table 1: Electrode-Pattern-Combination used for the pdp in Fig. 13

Implantation scheme	electrode	no.	patter no.
	TBPR4	15	222 
	TLL03	18	41 
	TLR01	22	308 

In Fig. 14 the PDP was applied to another electrode-pattern-combination. This time the occurrence of 5 different pattern has been observed. Thereby a seizure warning may be given when at least 3 of the studied 5 electrodes have shown the observed pattern. Table 2 gives the according pattern-electrode-combinations.

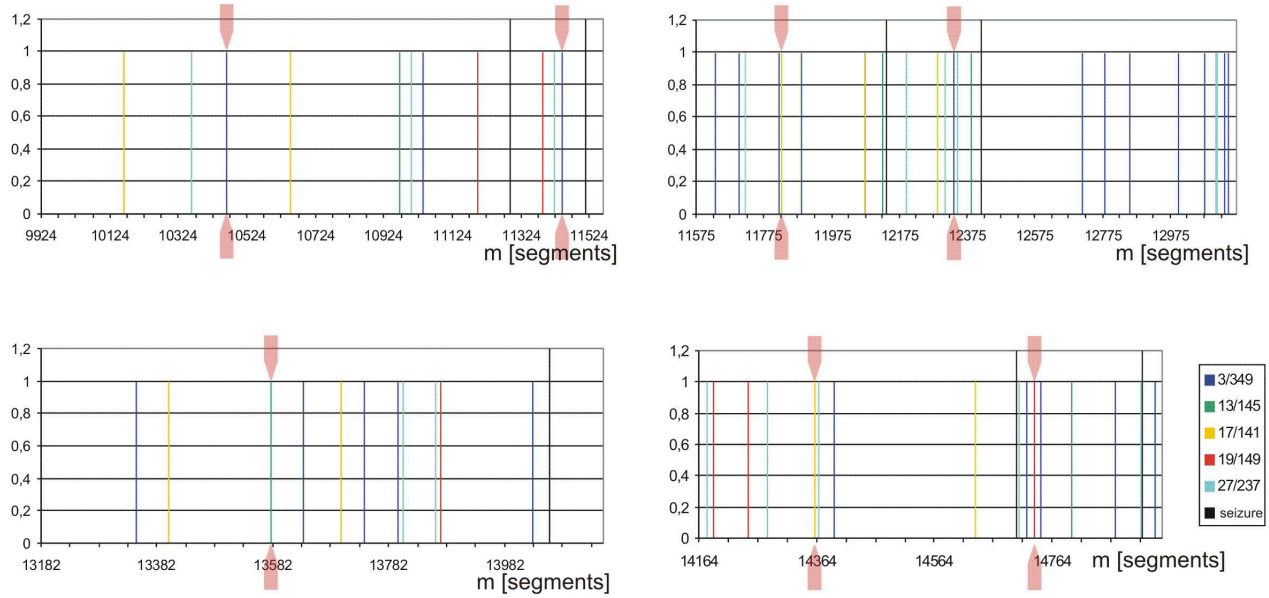
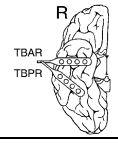
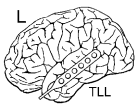
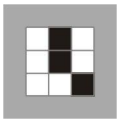
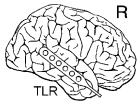
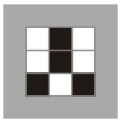
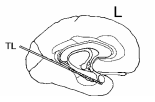


Fig. 14 : Results of the Pattern Detection Algorithm (PDP) based on five observed electrode points. Seizures are marked by black vertical lines, seizure warnings are marked by grey arrows. A seizure warning is given when the pattern has occurred at least in three of five electrodes before the seizure.

Table 2: Electrode-Pattern-Combination used for the pdp in Fig. 14

Implantation scheme	electrode	no.	patter no.
	TBPR1	3	349 
	TLL06	13	145 
	TLR04	17	141 
	TLR06	19	149 
	TL07	27	237 

Comparing the results for the two shown electrode-pattern-combinations leads to the statement that the found occurrence behaviour in both cases is very similar to each other. Both results show that the generalized pattern detection algorithm may possibly lead to a seizure precursor. This has to be verified by analysing long-lasting data sets of other patients.

5. Conclusion

In this contribution we presented an overview of our work analysing recordings of the electrocorticogram (ECoG) or the stereo-EEG (SEEG) in epilepsy. Several feature extraction algorithms possibly allowing seizure precursor detection have been discussed together with different results. Especially a prediction of EEG signals by means of Volterra systems and Discrete-time Cellular Nonlinear Networks have been treated. The results show distinct changes of features extracted from the obtained predictor coefficients for successive data segments of different electrodes. The observations seem to point to the occurrence of precursors of impending epileptic seizures. Furthermore a generalized pattern detection algorithm has been applied to long-lasting recordings of a certain patient. An automatic seizure warning given by a CNN based electronic device by an application of this algorithm seems to be possible also for this case. Nevertheless these results should be verified in current work by taking long-lasting recordings of more patients.

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