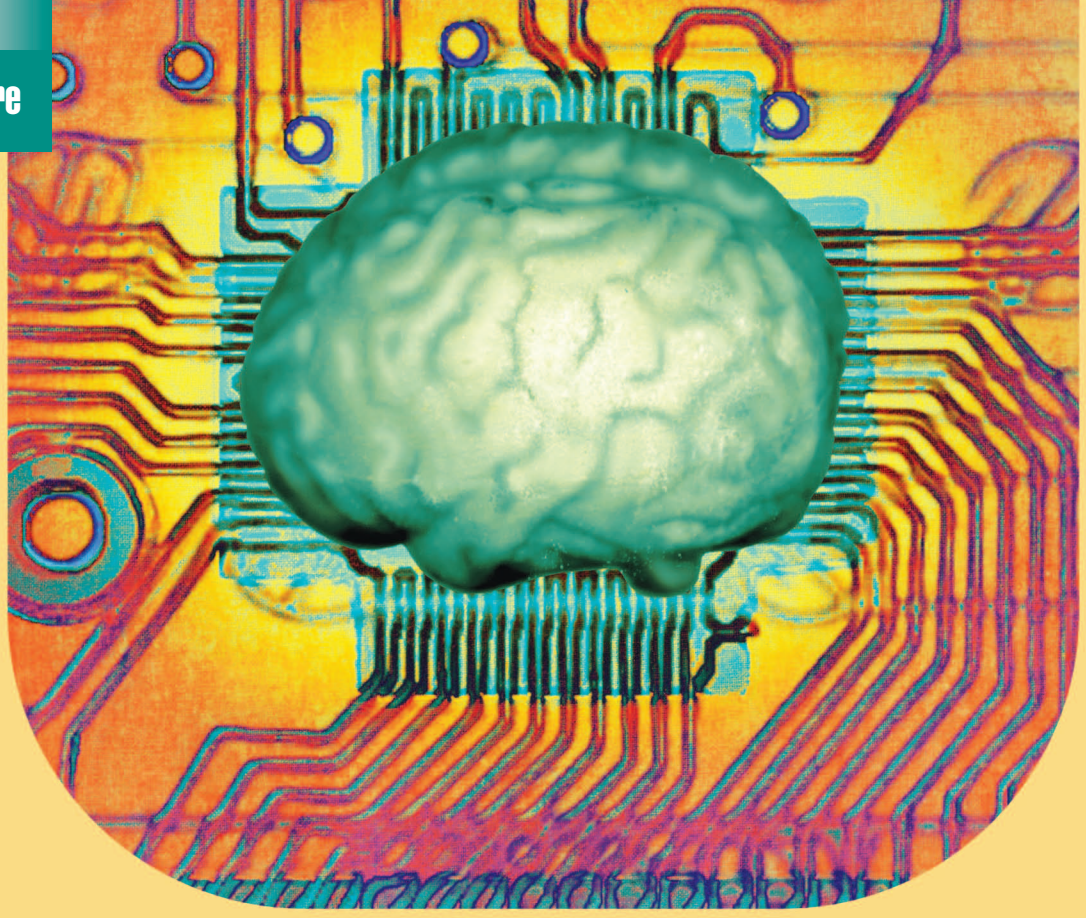

The Seizure Prediction Problem in Epilepsy: Cellular Nonlinear Networks

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Abstract

70 million people are affected by epilepsy which is the most common chronic neurological disorder worldwide. About 70% of patients can expect an effective seizure control with medication. The realization of an implantable device capable of detecting impending seizures, warning patients and rendering some kind of treatment would be of great benefit. In this contribution, a brief history of epilepsy and an introduction to terminology and symptoms are given followed by a short summary of current research going on in the field of seizure prediction. Afterwards, an introduction to Cellular Nonlinear Networks (CNN, a paradigm for high speed computation) is given and finally a presentation of 4 different CNN based approaches to epileptic seizure prediction will convey a vision of the methods possibly used one day on an implantable seizure warning device.

I. Patient Stories

A.

JA is a 45 year old man with a history of complex partial seizures since the age of 15. He has had a febrile seizure as an infant at age 18 months, but then developed normally. At age 25 he began to have staring spells during which he hummed, smacked his lips and wandered around the house. He was evaluated and no clear cause was found. He was treated with a number of medications, but his seizures continued to 3–4 times per month. JA eventually married, but never finished college. His seizures were too disruptive. He worked briefly at various odd jobs, but was never able to keep one for very long because of his epilepsy. He was followed at a local epilepsy center and enrolled in over 6 experimental trials of antiepileptic medication, none of which helped his seizures. As an adult JA mostly stayed at home, fearful of when his seizures might strike, because they would cause him to wander out of the house and into the streets in the neighborhood. He injured himself frequently, tripping, falling, and suffered fractures, burns, and lacerations. At age 35 JA was evaluated at a region epilepsy center and referred for surgery to remove part of his temporal and frontal lobes. Seizures were slightly worse after the surgery, and his behavior became impulsive.

Because of his wandering and the unpredictability of his seizures JA, now 46, locks himself in the house every day when his wife leaves for work. He puts the key in a series of four locked boxes, because he feels that these will be too complicated for him to get through to let him outside of the house during seizures and after then, during his period of post-seizure confusion. He continues to have impulsive behavior and 4–6 seizures per month.

B.

CL is a 30 year old single mother of 3 who lives alone with her children and has a 20 year history of seizures that come from both temporal lobes. She has been tried on seven different medications, each of which caused different side effects, but continues to have 2–4 seizures per week. Most of her seizures are staring spells lasting up to 2 minutes, but she has 2–3 generalized convulsive seizures per month, which have caused her to bite her tongue severely. CL has been unable to work since after high school and lives on social security and disability in public housing with her children. As early as 5 years of age her oldest child learned seizure safety and to call 911 for an ambulance when "mommy" did not awaken after a seizure for 10 minutes. CL has suffers several episodes of continued seizures, status epilepticus, for which she has been hospitalized each of the past 3 years. These illnesses have been followed by post-ictal psychosis, marked by hallucinations, delusions and confusion, and which have required hospitalization for several weeks at a time. CL's children have been placed into foster care on one occasion because of these episodes and her frequent events. CL has no warning before her seizures and cannot call for help. Her life is severely restricted and she relies on friends to help her shop, take her children places and to conduct many activities of daily living. Two years ago CL underwent intracranial electrode placement to evaluate her for epilepsy surgery, but was found not to be a candidate because the seizures were found to arise equally from both temporal lobes. CL has suffered from depression and contemplated suicide, but is getting therapy for this. She is currently taking experimental medication which is not controlling her.

C.

VJ is a young mother of 1, a nurse, and was born into a family in which she, her father and one sister have seizures. She has had these events since elementary school. Seizures come in flurried once or twice a month that can last all day. VJ has mild seizures that do not affect her awareness and warn her of bigger episodes, sometimes hours in advance. Because of this warning VJ has been able to drive and pull off the road when she feels a seizure coming on, she has been able to finish her nursing degree, work and have a child. VJ's seizures were not well localized on MRI scan or EEG and it was determined that surgery might contain more risk for her than potential benefit. It is thought that VJ's seizures come from her motor speech area, because she is alert but cannot speak during her mild events. VJ has been tried on 8 medications during her lifetime and none have controlled her completely. She currently takes 3 medications, which make her tired and sluggish in the morning, but she is grateful to be able to lead some semblance of a normal life. She states that knowing when her seizures are going to occur has enabled her to plan around them, and have a career, family and social life.

II. Epilepsy

Worldwide about 70 million individuals are affected by a neurological disorder named epilepsy. It is not limited to certain ages or groups; anyone can get

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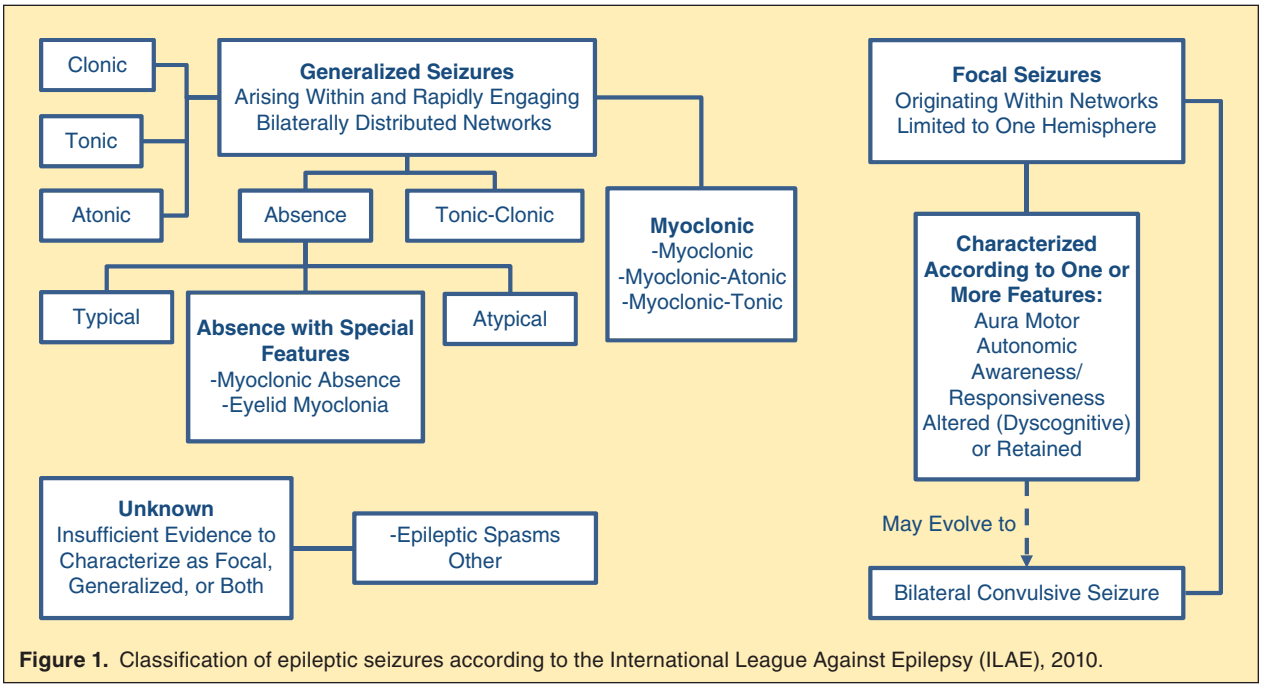

Figure 1. Classification of epileptic seizures according to the International League Against Epilepsy (ILAE), 2010.

epilepsy at any age. Epilepsy is not a specific disease, but it is known as a disorder of a brain characterized by recurrent seizures, i.e., the enduring predisposition to generate epileptic seizures and their associated consequences [78]. Epileptic seizures are the clinical manifestation of transient abnormal excessive or synchronous neuronal activity in the brain. The large variety of different kinds of seizures can be categorized into focal (partial) seizures which originate and remain in a circumscribed area of the brain and into generalized seizures involving almost the entire brain [15]. A more detailed classification of seizures has been published in 1970 by the International League Against Epilepsy (ILAE) being updated in 1981 by a second classification scheme generally accepted up to now. A report about a further revision of the terminology and concepts for organization of seizures and epilepsies has been given by the ILAE [4] in 2010. Focal seizures can be simple or complex, where consciousness and memory is not impaired during simple partial seizures. On the other hand, an alteration of consciousness and memory can be observed for complex seizures. Very often patients have an aura, i.e., a seizure warning e.g., in the form of distorted sensory perceptions or in the form of a familiar feeling: a déjà vu event. Furthermore, many patients (about 75%) show automatisms during complex seizures with automatic fragments of different forms of activity including lip smacking, swallowing, chewing, and licking motions but also walking around aimlessly and/or absurd and/or aggressive behavior. A focal seizure can spread over the entire brain leading to a tonic-clonic seizure, i.e., it evolves to a secondarily generalized seizure. In comparison to this development, from the beginning large brain areas are affected in primarily generalized seizures which may be divided into different categories given in Fig 1. In a generalized tonic-clonic seizure, which was previously called grand mal seizure, the majority of seizures start with a loss of consciousness and a sudden tonic activity, where the body becomes rigid (stiffening of muscles) and the patient falls to the ground. There is a cry or moan if respiratory muscles are contracted in the tonic phase. In this period or in the postictal phase[1] incontinence [73] can occur. The rigidity then evolves into a generalized jerking—the clonic phase. Frequently cyanosis, salivation, and tongue biting [14] can be observed during a seizure. Consciousness slowly returns after a variable time period in the postictal phase followed by a recovery phase lasting from minutes to hours. A detailed description of other types of generalized seizures can be found in [14], [73].

III. History

Written more than 3000 years ago, an Assysrian-Babylonian text for the first time provides a description of some seizure phenomena. It is known that also physicians of China and India were familiar with epilepsy in this time period. The word epilepsy is derived from the

[1]The period after a seizure.

Greek verb epilamvanein [14] meaning "to be seized," "to be taken hold of," or "to be attacked," as a consequence of the Greek's belief that an individual having a seizure—usually believed as a punishment—is possessed by a god or a spirit. Although, it was believed in common that epilepsy is as sacred disease, Hippocrates (c. 460-377 BCE) underlined in his famous treatise *On the Sacred Disease* [33] that it has nothing to do with spirits and demons. Especially he suggested that seizures are originated in the brain. Unfortunately, his work had a small influence on the general belief only that epilepsy is caused by supernatural forces. While for a very long time no significant progress had been made, Thomas Willis (1621–1675) [14] suggested that epilepsy is originated in the brain but in the form of "animal spirits" moving from the brain to peripheral nerves. He believed that a centripetal movement of an animal spirit could lead to an explosion in the brain resulting in a convulsive epileptic seizure. Further progress was based on the work of Luigi Galvani (1737–1798), who discovered that a frog muscle could be made to contract by electricity. In a long term controversy Alessandro Volta (1745–1827) disputed his interpretation of obtained results. It was not before the 19th century, however, that the belief in supernatural forces faded out and new theories have been developed. Robert Bentley Todd (1809–1860) collaborated with Michael Faraday (1791–1867), an outstanding pioneer in electricity, and he firstly recognized the role of electrical discharges in epilepsy. Tremendous efforts have been made by John Hughlings Jackson (1835–1911) in clinical observations. In 1870 he emphasized [39] that "A convulsion is but a symptom, and implies only that there is an occasional, an excessive, and a disorderly discharge of nerve tissue on muscles." Furthermore, following his ideas about cerebral localization [79], the nervous system has a three level hierarchical structure where each element of the lowest level represents a certain body part. The view of a localized representation of motor functions was supported by experiments of Fritsch and Hitzig [24] which were published in 1870. They found that stimulating motor cortex in dogs immediately resulted in motor responses, which muscles twitched depending on the placement of the stimulating electrodes. Especially, Richard Caton (1842–1926) observed in his animal experiments electrical activity of the brain and discovered that brain stimulation will lead to an electrical response of the brain, i.e. an evoked potential. With his results he provided an important basis for the work of Hans Berger (1873–1941), the inventor of electroencephalography. The discovery of Berger described in his famous publication [5] in 1929 can be regarded as a historical breakthrough and an important step to modern clinical technology. It was a long winding road from myths and demonizing to a better understanding of epilepsy based on research.

IV. Seizure Prediction

The development and implementation of methods allowing a reliable prediction[2] of epileptic seizures has been addressed in numerous investigations starting about 1975. A fascinating vision might be the realization of a small warning system improving considerably the life quality of patients by preventing them from injury and removing the uncertainty of a sudden seizure onset at any place and/or time. Despite tremendous efforts in the past 5 decades [6] which had led to clearly improved therapies based on antiepileptic medications, at least for 30% of patients an effective control of seizures cannot be provided by antiepileptic drugs. Furthermore, the application of seizure prediction could lead to reduced side effects as, e.g., sedation and clouded thinking, if on-demand short-acting drug release and electrical stimulation [49] could be envisaged. It can be envisioned that a warning system detects a pre-seizure phase and afterwards trigger a certain treatment in order to stop the seizure generating process. Finally, research in the context of developing seizure prediction systems will lead to an improved understanding of mechanisms and phenomena in epilepsy.

For a long time it has been believed that there is no transition from an interictal[3] phase to a seizure, i.e., the seizure onset has been regarded to be an abrupt phenomenon. Recent [66] results of different investigations give evidence that at least for certain seizures a transition before a seizure onset can be detected by analyzing signals of an electroencephalogram (EEG)—in the following called EEG signals for the sake of simplicity [53]. For example, following Lehnertz et al. [49], a seizure-initiating process in a focal epilepsy can be regarded as a process of an "increasing number of critical interactions between neurons in a focal region and connected units in an abnormal functional network unfold over time." Though the prediction problem has been treated for a long time in many investigations, up to now there is no method allowing an automated seizure prediction with sufficient sensitivity and specificity required for broad clinical application. Especially, usually the development and performance evaluation of methods will be performed retrospectively by analyzing signals of EEG recordings with known seizure onsets. However, clinical usefulness and reliability should be proved in blinded, prospective, and randomized trials.

[2]In literature anticipation or forecasting will be used as well, despite their different meanings, for tackling the same problem.
[3]The time period between seizures.

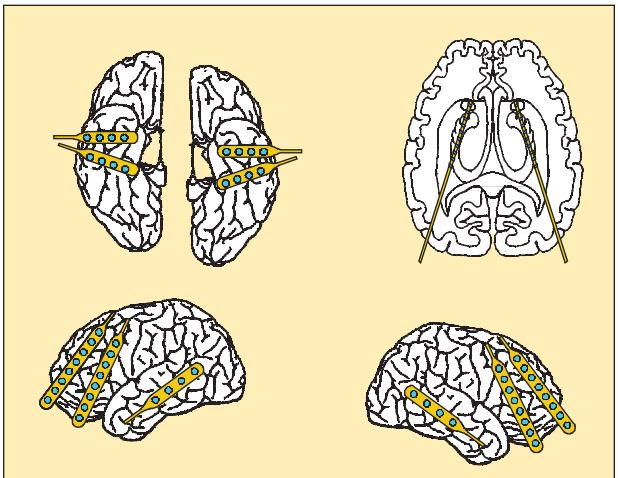

Figure 2. Typical example of an implantation scheme.

Various univariate and multivariate features of EEG signals involving linear and nonlinear methods have been derived and applied for seizure prediction. Usually, a measure as an EEG characterizing quantity will be determined in a retrospective analysis by using segmented data of one (univariate) or more (multivariate) positions of intracranial EEG recordings[4]. A typical implantation scheme is shown in Fig. 2. Typically, time series are obtained consisting of values of EEG characterizing quantities which are studied, in order to determine changes in the temporal evolution, undoubtedly aimed to uncover the development to a pre-seizure state. Some linear and nonlinear features which have been studied for seizure prediction are given in Table 1. In recent work [11], [20], [21], [30], [70] combinations of different methods have been applied to improve the seizure prediction performance.

Promising candidates for EEG feature extraction as well as for an envisioned realization of a miniaturized seizure warning system are Cellular Nonlinear Networks (CNN). Since CNN have been proposed by Chua et al. [9], these networks have been developed into a paradigm for universal high-speed computation. Generally, they consist of locally coupled dynamical systems which may exhibit different nonlinear phenomena as wave propagation (e.g., solitons [19], autowaves, spiral waves, and scroll waves [10]), oscillations of coupled oscillators [65], and spatio-temporal chaotic behavior. Moreover, it is known for a long time that CNN are well suited to solving PDE [26], [76]. According to Chua [10], a CNN is defined by:

1) "A spatially discrete collection of continuous nonlinear dynamical systems called cells, where information can be encrypted into each cell via three independent variables called input, threshold, and initial state."
2) "A coupling law relating one or more relevant variables of each cell C_{ij} to all neighbor cells C_{kl} located within a prescribed sphere of influence $S_{ij}(r)$ of radius r, centered at C_{ij}."

An illustration of the CNN coupling structure for $r = 1$ is given in Fig. 3. Numerous investigations are based on translation invariant state equations like

$$\dot{x}_{i,j}(t) = -x_{i,j}(t) + \sum_{k,l \in N_{i,j}(r)} a_{k,l} y_{k,l}(t) + b_{k,l} u_{k,l}(t) + z$$

of the so-called Chua-Yang model [9]. Here, $x_{ij}(t)$ denotes the state, $y_{ij}(t)$ *is* the cell output, and $u_{ij}(t)$

Table 1.
Linear and nonlinear features for seizure prediction.

Univariate Measures	Multivariate Measures
Short-term fourier transform [29], [31]	Synchronization [57]
Accumulated energy [34], [35], [40]	Nonlinear interdependence [42], [43], [44]
Autocorrelation and autoregressive modeling [11]	Autoregressive measures of synchrony [11]
Statistical moments [54]	Phase synchronization [7]
Correlation dimension [46], [47], [48]	Dynamical entrainment [35]
Correlation density [56]	Similarity index [51], [52]
Kolmogorov entropy [12]	Simulated neuronal cells [70], [78]
Dynamical similarity index [50], [59]	Linear and nonlinear prediction by cellular nonlinear network [27], [60]
Loss of recurrence [62], [63]	System identification by cellular nonlinear networks [27]
Lyapunov exponent [36], [37], [38]	

[4]Today, studies are mainly based on intracranial EEG recordings obtained in clinical evaluations of patients for resective surgery.

represents the input of a cell C_{ij}. The neighborhood of C_{ij} is given by

$$\mathcal{N}_{i,j}(r) = \{C_{k,l}: \max(|k-i|,|l-j|) \le r,\ 1 \le k \le M, 1 \le j \le N\}$$

and usually the cell output by

$$y_{i,j}(t) = f(x_{i,j}(t)) = \frac{1}{2}(|x_{i,j}(t)+1| - |x_{i,j}(t)-1|).$$

Especially, by endowing a CNN cell [69] with local analog and logic memory, communication circuitry and units, a so-called CNN universal machine has been invented. In the following years, several CNN based miniaturized realizations with stored programmability have been developed. For example, recently the EyeRis 1.3 system, the MIPA4k, and SCAMP-5 have been introduced which are sensor-processor systems for high speed vision. Details of these systems can be found elsewhere [13], [64], [68]. Applications of CNN can be found in a wide range of interdisciplinary research including image and video processing, the realization of bio-inspired and nanoscale systems, and feature extraction in epilepsy [1], [2], [3], [23], [25], [27], [45], [67], [77]. Miniaturized CNN realizations may provide a technology to integrate to a large extend all necessary processing steps, e.g., multi feature extraction, classification, and to trigger different stimulation techniques, towards an implantable medical device.

In several investigations [8], [27], [42], [43], [44], [60], [61], [74] CNN have been considered for feature extraction in epilepsy. It has been shown that the correlation dimension approach can be transferred to CNN [45] with nonlinear weight functions. Furthermore, CNN have been used for the estimation of nonlinear interdependencies [43], [44] and phase synchronization [74]. While in these investigations CNN versions of existing feature extraction methods have been determined and analyzed in detail, a new data based identification by CNN has been proposed by Gollas et al. [27]. Furthermore, promising results have been obtained by applying

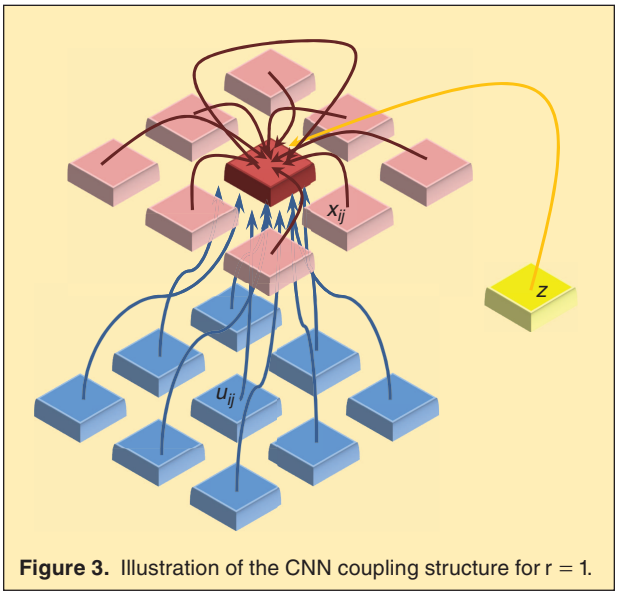

Figure 3. Illustration of the CNN coupling structure for r = 1.

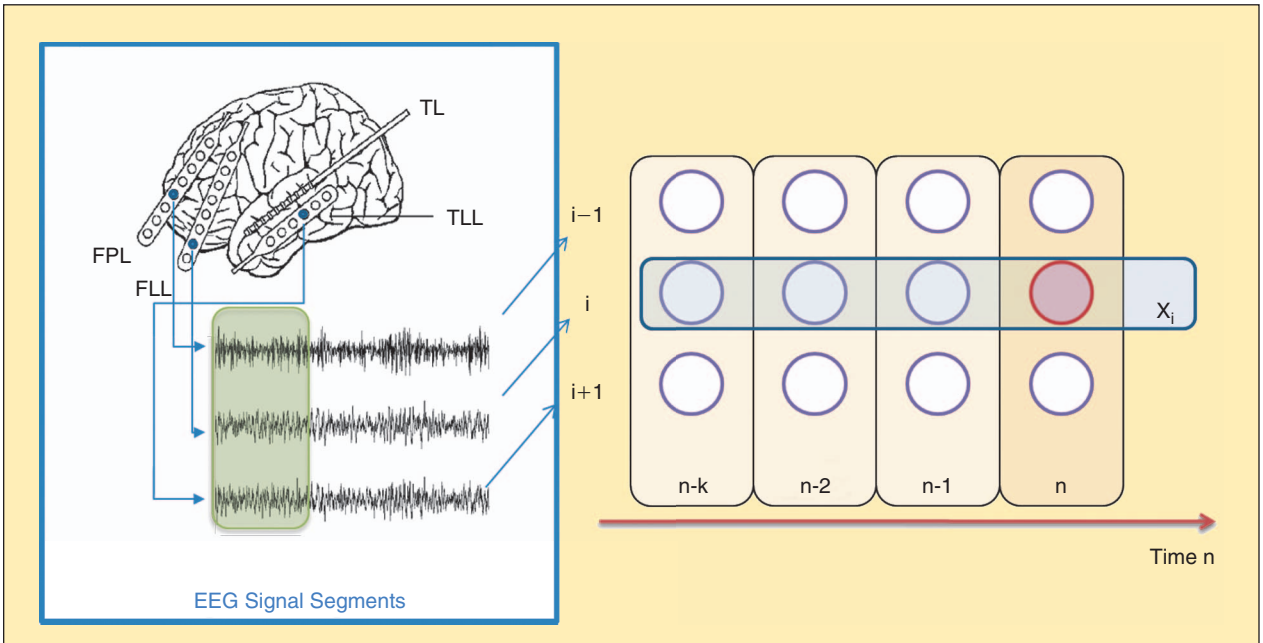

Figure 4. Scheme of CNN based signal prediction. K = 3 values of 3 channels are used for the prediction of a signal value $\hat{x}_i(n)$ with values of channel $x_i(n)$ also used in the prediction.

a multivariate nonlinear prediction of EEG signals [60], [61]. The distinct feature of all these investigations is that they are based on CNN with polynomial weight functions which are defined according to

$$\dot{x}_{i,j}(t) = -x_{i,j}(t) + \sum_{k,l \in N_{i,j}(r)} \mathcal{P}_{k,l}(y_{kl}(t)) + \mathcal{P}_{k,l}(u_{k,l}(t)) + z$$

with

$$\mathcal{P}_{k,l}(y_{k,l}(t)) = \sum_{p=1}^{P} a_{k,l,p}[y_{k,l}(t)]^p$$

and

$$\mathcal{P}_{k,l}(u_{k,l}(t)) = \sum_{p=1}^{P} b_{k,l,p}[u_{k,l}(t)]^p.$$

In the following, the multivariate signal prediction, the system identification, and correlation dimension approach based on CNN shall be described.

The results discussed here were obtained using a data base of both long term and short term intracranial EEG recordings of more than 20 patients suffering from focal temporal lobe epilepsy. All of the recordings were acquired in presurgical diagnostics at the Clinic of Epileptology in Bonn. They are sampled at 200 Hz and have been taken from up to 53 electrode channels. Long term recordings usually cover about 100 h of nearly continuous EEG recordings containing between 4 and 10 seizures for each patient.

V. Spatio-Temporal Signal Prediction in Epilepsy by Delay-Type Discrete-Time Cellular Nonlinear Networks (DT-CNN)

In this approach, DT-CNN is used to process EEG signals as shown in Figure 4. EEG signals recorded from different locations of the brain are divided into quasi-stationary segments of 5 s to 10 s lengths, which for our data means N = 1000 to N = 2000 values each. Those segments are then processed by DT-CNN following the state equation[5]

$$\hat{x}_i(n) = \sum_{\lambda} \sum_{\kappa=1}^{K} \sum_{p=1}^{P} a_{\lambda,\kappa,p}\, x_\lambda (n-k)^p,$$

where K signal values of Λ electrode channels are used to predict values of a certain channel x_i that may or may not be included within those channels. The polynomial order of the prediction can be varied and is denoted by P. For each value of the segment, one iteration of the DT-CNN is carried out. The example in Figure 4 shows a prediction using K = 3 values of Λ = 3 channels for the prediction of a signal value $\hat{x}_i(n)$ with values of channel $x_i(n)$ also used in the prediction.

This can be done by introducing a supervised optimization process [60], applying a wide variety of optimization strategies, in regard to the root relative mean square error of a signal segment given by

$$e = \sqrt{\frac{1}{N} \sum_{n=1}^{N} \frac{(\hat{x}_i(n) - x_i(n))^2}{\overline{x_i^2}}}.$$

Additionally, by introducing correlation functions of two time series $x_i(n)$ and $x_l(n)$ as

$$\psi_{i,l}(n-m) = E\{x_i(n), x_l(m)\},$$

the predictor coefficients a can be derived by solving a linear equation system [27], [72], given by $M \cdot a = \Psi$, where M is a matrix containing correlation functions, a represents a coefficient vector and Ψ is a vector containing cross correlation functions of each channel used for the prediction and the channel that is predicted.

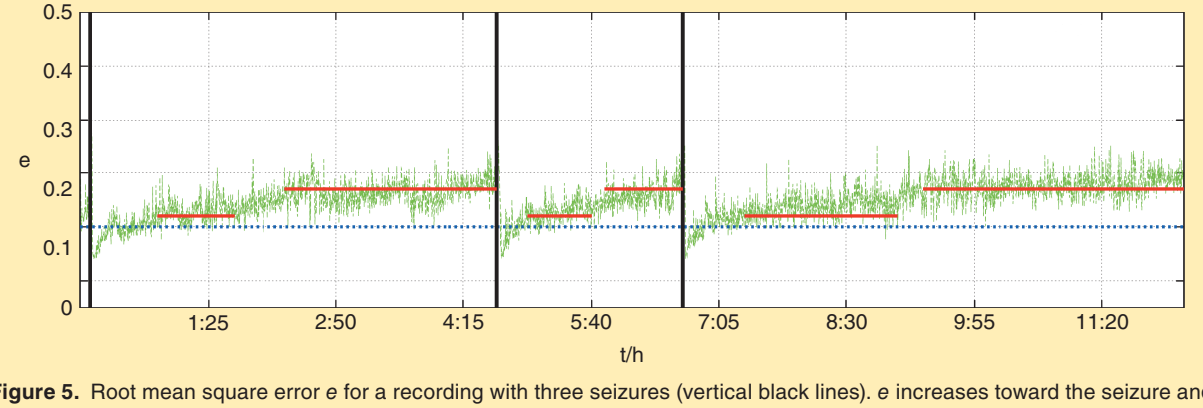

Figure 5. Root mean square error *e* for a recording with three seizures (vertical black lines). *e* increases toward the seizure and exceeds the interictal mean (dotted blue line).

[5]For the sake of simplicity, the cell index *i* will be used instead of *i,j*.

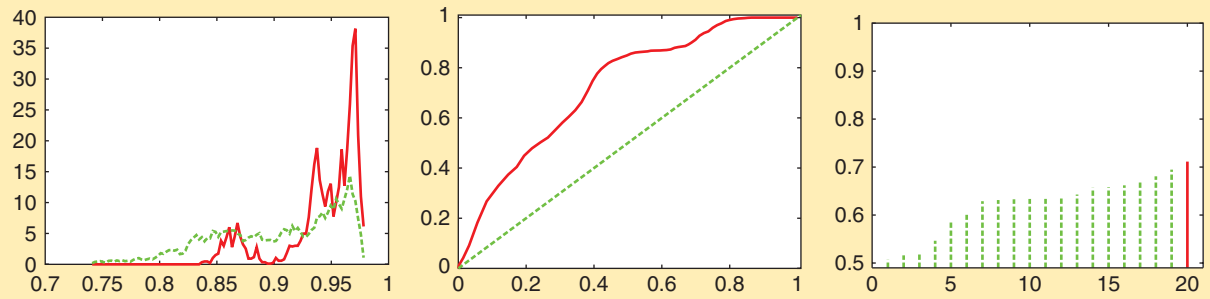

Figure 6. Results of an ROC analysis of e, AUC = 0.71. Left: error distributions for interictal and pre-seizure periods, middle: ROC curve, right: AUC values of surrogate and real data.

This predictor has been studied in detail by varying polynomial order, prediction order and different neighborhoods. It has been discovered that even with a very simple linear predictor which only considers signals of neighboring electrodes and a time delay of one, a very interesting behavior of the predictor prior to a seizure can be found. Before each of the seizures a sharp increase of the prediction error followed by a drop after the actual seizure could be observe. Figure 5 shows an example recording depicting this kind of behavior within an EEG recording of about 12 hrs length. The error e over time is given as a light green line. Additionally, the interictal mean value for recordings without a seizure is given as a blue dotted line. Red lines show temporary means that clearly are above the interictal means for 2 hrs previously to the 2nd seizure and 50 min before the 3rd seizure. The rise of the mean error indicates a seizure that occurred directly after the end of the recording depicted followed by a pre-seizure period of 2 h and 45 min. This kind of behavior has been found for many analyzed patients with varying strength of significance in terms of possible indicators of a pre-seizure state and which also depends on the location of the channel used for the prediction [27], [60]. Current research now focuses on the choice of channel combinations which potentially show distinct changes prior to a seizure. It is assumed that the coupling of channels from different regions of the brain varies with time. Since an epileptic seizure is characterized by a change of synchronization of various regions of the brain, a change in the coupling of channels recorded at different locations might indicate a pre-seizure state [71].

To evaluate the significance of all measures discussed here [58], two methods of statistical evaluation have been applied. Firstly, the so-called AUC value, a measure taken from an approach well known as receiver-operating characteristics (ROC) analysis, has been calculated [18], [75]. The AUC value of 0.5 indicates a measure that is equal to (uniformly distributed) chance, a value larger than 0.5 indicates that a measure is capable of discriminating between an interictal and pre-seizure state. Additionally, 19 sets of so-called surrogate data are generated. Different approaches to the generation of such data have been proposed by various authors [22], [58]. Here, we used surrogate data in which the onset times of seizures have been arranged in a random manner [41]. Results of any method were considered to be significant only if all AUC values obtained from surrogate data are lower than those of the actual patient data. An example of such statistical evaluation of a CNN based signal prediction in which 3 neighboring electrode channels were used for the prediction is shown in Fig. 6. On the left, the error distributions of the error e of interictal periods (green) and pre-seizure periods (red) are depicted for a seizure prediction horizon of $h = 60$ min. The center image shows the ROC curve of the measure (red) which is clearly above the green line depicting an AUC value of 0.5. On the right, AUC values of all 19 surrogate data sets (green) and the AUC value of the real data (red) is given. Even though some AUC values obtained from surrogate data rise above the value of 0.5, the AUC value obtained for the real EEG recording is clearly larger than the largest value obtained for surrogate data [27].

VI. Identification of EEG-Signals by CNN

The modeling of neuronal systems in general and especially of activity associated with epilepsy has been a vital topic of research of various groups [55], [80]. In our approach, the aim is to find a model with complexity as low as possible which nevertheless can be used to model the transition of the dynamical system underlying EEG signal evolving from interictal pre-seizure activity. In order to derive a CNN based model of brain activity, we used so-called Reaction Diffusion CNN (RD-CNN) which have been shown to be able to display a wide range of complex behavior. We used polynomial coupling functions capable of representing a wide range of nonlinear behavior by means of a power series

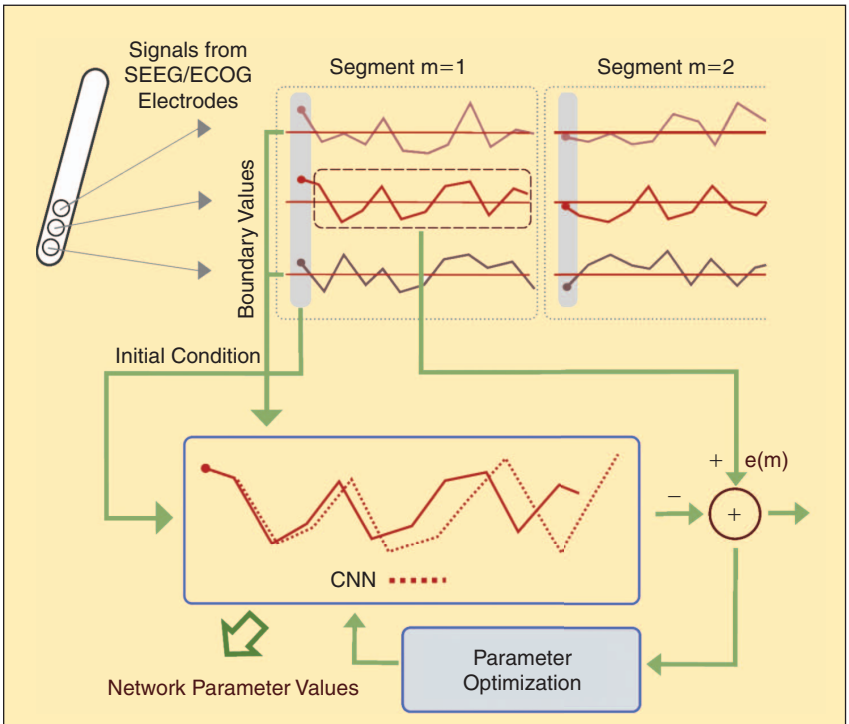

Figure 7. Scheme of the CNN algorithm for blind identification of EEG signals using RD-CNN. Neighboring channels are mapped onto neighboring cells. Then, a CNN parameter set capable of modeling the dynamics of the underlying the EEG signal segment is obtained.

expansion [28]. The CNN state equation of a layer l of such a CNN with L layers in total is given by

$$\dot{x}_{l,i} = f_l(x_{l,1}(t), x_{l,2}(t), x_{l,3}(t) \ldots x_{l,L}(t)) + D_l \overline{\nabla}^2 x_l(t).$$

Regarding the identification of brain electric signals, no underlying system can be derived directly. Therefore, a concrete representation of the functions $f_l(\cdot)$ has to be found using an optimization process. Taking into account only local couplings, a power series representation of the functions can be assumed as

$$f_l(\cdot) = \mathcal{P}_{l,l}(\cdot) + \mathcal{P}_{l,l-1}(\cdot) + \mathcal{P}_{l,l+1}(\cdot).$$

Figure 7 shows a scheme of the identification process using CNN. Quasi-stationary segments of EEG signal recordings of up to 10 s length have been used. Then, a parameter optimization with regard to the relative root mean square error is carried out. This again leads to time series of CNN parameters and error values e that can be analyzed in order to find distinct changes prior to a seizure.

Figure 8 shows typical results of such a process for a CNN of polynomial order $P = 3$. The result of an identification process of a CNN following the state equation of

$$\dot{x}_l(t) = \sum_{p=1}^{P=3} a_p x_i^p + D\nabla^2 x_i(t)$$

is shown along with the estimated values of a CNN based linear signal prediction [27]. Error values vary slowly over time and even though—in case of the left example—error values of the linear signal prediction

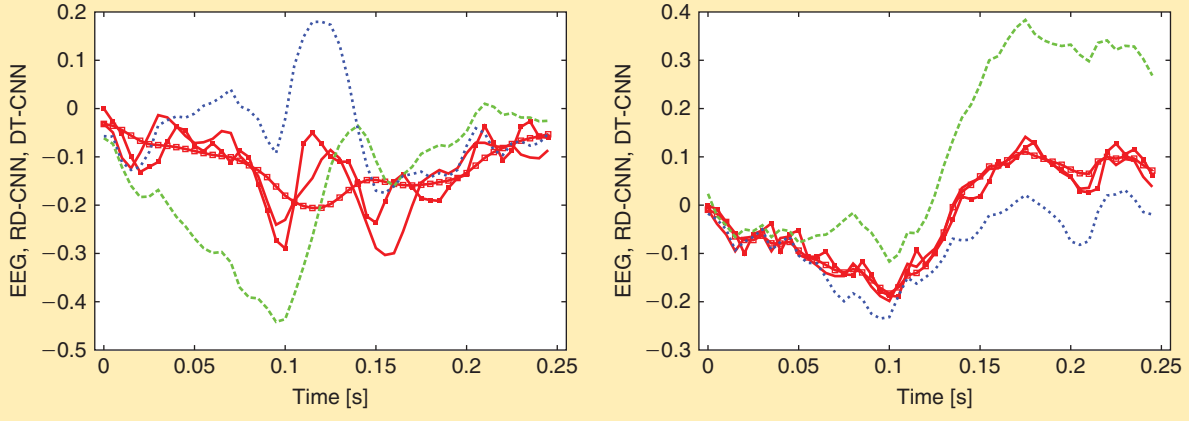

Figure 8. Cell outputs (□) of determined RD-CNN, estimated values (■) of the DT-CNN predictor together with signal values of the approximated EEG signal (—) and those of neighboring electrodes (----) and (····). Two segments with different error values. Left: $e_{pred} = 0.363$, $e_{ident} = 0.411$; right: $e_{pred} = 0.247$, $e_{indent} = 0.142$.

Table 2.
Influence of the polynomial order of both cell feedback P and neighboring couplings of a cell P_D to the mean square error.

	$P_D=1$	$P_D=2$	$P_D=3$	$P_D=4$	$P_D=5$	$P_D=6$	$P_D=7$	$P_D=8$
$P=1$	0.553060	0.407094	0.371738	0.373991	0.334633	0.308310	0.288700	0.273802
$P=2$	0.427972	0.373961	0.329795	0.334265	0.292390	0.290451	0.281247	0.267392
$P=3$	0.366183	0.323929	0.295558	0.287398	0.276862	0.277051	0.276716	0.243809
$P=4$	0.392346	0.326408	0.288364	0.258347	0.264322	0.275421	0.258108	0.262506
$P=5$	0.356876	0.296847	0.302006	0.278714	0.276380	0.247402	0.231866	0.235688
$P=6$	0.342840	0.281476	0.275603	0.268526	0.256282	0.262545	0.223685	0.236095
$P=7$	0.325110	0.292070	0.273210	0.240251	0.256868	0.224650	0.257639	0.234809
$P=8$	0.333395	0.280435	0.260762	0.238250	0.230291	0.240105	0.229042	0.222546

are slightly lower than for the identification of CNN, in general satisfying results have been obtained.

Table 2 gives an overview of the influence of the polynomial order of both cell feedback and neighboring couplings of a cell to the mean square error. As the error values for segments of EEG data vary strongly, 20 segments of EEG data of N = 50 values were used to calculate the error and then its mean was used in Table 2. The error decreases as the polynomial order increases and the polynomial order of the neighboring coupling has a slightly larger influence on the error than the polynomial order of the feedback coupling of the cell.

Additionally, Fig. 9 shows another example of cell output values $x_i(t)$ (-□-) and reference values of EEG. In this example, only a period of 1 s of the recording has been used as reference for the identification process. It can be seen that the CNN parameters found within the identification process are also suitable for modelling EEG data not used within the identification process.

Both parameter values of the CNN as well as the error time series have been taken into account in the analysis. First results indicate that the obtained error e can also be used for the detection of pre-seizure changes. For a seizure prediction horizon of $h = 10$ min AUC values of up to 0.77 have been be obtained.

VII. Correlation Dimension Approach

Several investigations [16], [17], [46], [47], [48] have shown that the so-called effective correlation dimension D_2^* allows a characterization of an epileptic process for successive segments of EEG signals in many cases. In order to enable an extraction of this feature by an implantable CNN-based device, different methods of approximating the effective correlation dimension by CNN output values have been derived. In the following, CNN with polynomial weight functions with polynomial orders up to P = 9 and with a neighborhood radius of r = 0 up to r = 4 have been considered within a supervised optimization process (see Fig. 7).

As outlined in [45], an EEG segment of N = 5184 normalized values—corresponding to a CNN with 72×72 cells—is taken as initial condition of a CNN, the output of which then is used as initial condition by a second CNN network performing a simple diffusion operation which

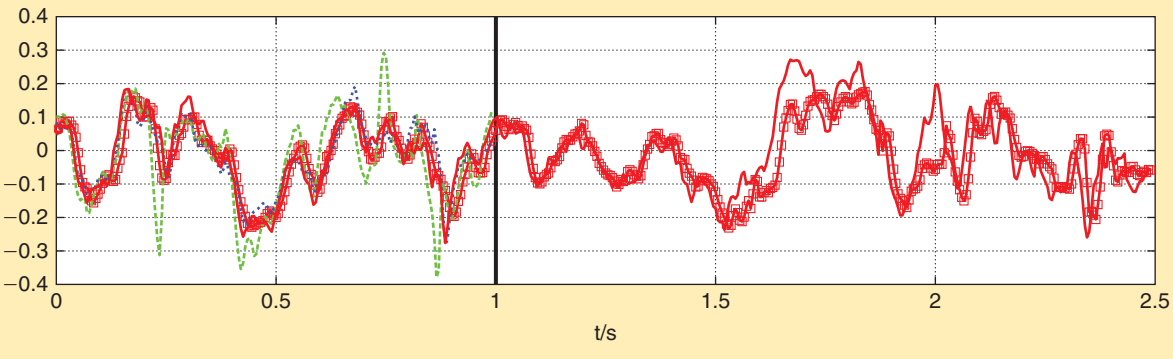

Figure 9. Cell output values of an RD-CNN with polynomial order P = 3 (-□-□-□-) compared to the reference EEG signal (—). Only a period of 1 s was used in an identification process. Additionally, neighboring electrode signals (----) and (·····) are shown for the identification period.

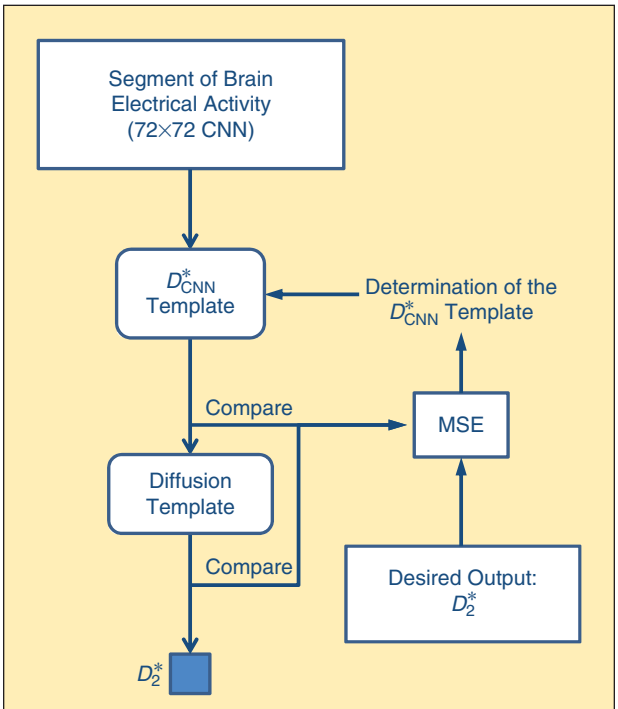

Figure 10. In a first step, D_2^* is the desired output for all cells of the first CNN and a mean square error is computed. The nonlinear weight functions of the first CNN are changed accordingly. In a second step, a diffusion operation is carried out and the homogenous gray scale value is compared to D_2^*. Again, only the weight functions of the first CNN are changed in order to optimize the result.

results in a constant grey value throughout the CNN that corresponds to the effective correlation dimension.

This method was tested on short term recordings of intracranial EEG taken from our data base and led to a mean error of less than 8%, even if using very different recordings for testing and training the algorithm. Remarkably, for most cases an increase of the polynomial order of the CNN did not lead to an increased accuracy and only a very small training set of EEG segments is necessary to obtain a high accuracy [45].

VIII. CNN-Based Pattern Detection in Epilepsy

In the context of epileptic seizure prediction, the phrase "pattern detection" usually is associated with the detection of distinct features of the signal which can be used for the prediction of a seizure, such as peak and drop occurrences, increasing peak frequency and so forth. In our approach, we used a CNN pattern detection algorithm based on a statistical level-crossing analysis of EEG-signals.

The main idea of pattern detection for predicting epileptic seizures supposes that involved areas of the brain are changing their usual way of acting and entering another state of behavior. A second presumption is that these behavior alterations could be imaged by occurrence or non-occurrence of specific patterns which represent different level-crossing behavior of a signal. Therefore, two types of behavior can be taken into account: Certain patterns occur mainly in a preictal phase. A detection of those patterns could mark an upcoming seizure. In contrast to that, other patterns occur frequently throughout interictal phases but rarely during pre-ictal periods [23]. The non-occurrence of such patterns for a certain time could also be taken as a marker for an impending seizure. Though theoretically detecting such behavior from the data of just one electrode point would be enough for successful seizure anticipation, the exploration of several data sets has shown that different behavior can be observed for data taken from different electrodes, depending on the pattern.

IX. Conclusion

We have shown that CNN represent a powerful tool for the extraction of EEG signal features in epilepsy. Computing structures based on CNN are promising candidates for the envisaged vision of a realization of a miniaturized seizure warning and prevention device. A CNN based signal prediction approach, an EEG signal based identification by CNN, a correlation dimension based approach, and a pattern detection by CNN have been proposed for feature extraction and for the characterization of spatiotemporal properties of different brain areas in focal epilepsies. Although, obtained results are promising and indicate that these methods may be considered for a future implantable device, prospective verification studies are necessary to prove their usefulness for a broad clinical application.

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