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A CNN-Based Synchronization Analysis for Epileptic Seizure Prediction: Inter- and Intraindividual Generalization Properties

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Abstract— **We investigate the generalization capability of our recently proposed CNN-based approach to measure the strength of generalized synchronization in EEG recordings from epilepsy patients. With an in-sample optimization on short-lasting EEG data taken from two recording sites of a single patient we obtain a CNN with polynomial-type templates that allows us to approximate the strength of generalized synchronization in continuous long-lasting multichannel EEG recordings from this patient at a high accuracy. In an out-of-sample study we use the same CNN to analyze days of multichannel EEG data from other patients and observe that the strength of generalized synchronization between different brain regions in different patients can be approximated with a sufficient accuracy. These inter- and intraindividual generalization properties render CNN highly attractive for the development of miniaturized seizure prediction devices.**

I. Introduction

Understanding complex synchronization phenomena between dynamical systems is an active field of research in many scientific and technical disciplines [1], [2]. Over the past decade different frameworks for the mathematical description of synchronization in dynamical systems have been developed, which have led to the proposition of different concepts of synchronization. The concept of *generalized synchronization* was introduced for driver-responder systems to describe a state in which the state variables of the systems are connected by some functional relationship with certain mathematical properties [3], [4], [5]. Quantification of generalized synchronization is usually based on specific topological properties of the state spaces that were reconstructed from the signals [6]. In Ref. [7] we proposed the nonlinear interdependence as a robust measure for generalized synchronization between two time series. This measure does not assume a functional relationship between the dynamics of the underlying systems.

Synchronization phenomena play a crucial role in the human brain. Neuronal synchronization ensures the normal functioning of the brain while a substantial change in neuronal synchronization may give rise to malfunctions such as the disease epilepsy along with its cardinal symptom, the epileptic seizure. Although there are numerous studies exploring basic neuronal mechanisms that are likely to be associated with seizures, to date no definite information is available as to how or when or why a seizure occurs in humans. If it were possible to identify pre-ictal precursors from the EEG of epilepsy patients, therapeutic possibilities and thereby the quality of life could improve dramatically for epilepsy patients [8]. The last three decades have witnessed a rapid increase in the development of new EEG analysis techniques that appear to be capable of defining seizure precursors. Since the 1970s studies on seizure prediction have advanced from preliminary descriptions of pre-ictal phenomena and proof of principle studies via controlled studies to studies on continuous multi-day recordings (see Refs. [9], [10], [11], [12] for an overview). There is now strong evidence that particularly EEG analysis techniques that characterize complex synchronization phenomena between different brain regions show a promising seizure prediction performance that exceeds chance level if tested by statistical validation [13], [14], [15], [16].

In Refs. [17], [18], [19], [20] we proposed to approximate strength and direction of generalized synchronization as well as other types of synchronization with polynomial-type CNN, and exemplary applications to EEG recordings from epilepsy patients indicated the high relevance of our approach to improve the detection of long-lasting pre-seizure states. We aimed at extending our previous work by evaluating inter- and intraindividual generalization properties of our CNN-based approach to approximate the strength of generalized synchronization in long-lasting multichannel EEG recordings from ten epilepsy patients.

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II. METHODS

A. EEG Database

We here investigated multi-day EEG recordings (6.9 ± 1.6 days) from ten epilepsy patients undergoing presurgical evaluation for resective therapy of pharmacoresistant temporal lobe epilepsy. The data were recorded from bilaterally implanted intrahippocampal depth electrodes, each consisting of ten sensoring contacts, and were sampled at 200 Hz within the frequency range 0.5-85 Hz using a 16 bit ADC. During monitoring a total of 60 seizures occurred. To process the data we used a moving-window technique (non-overlapping segments of 4096 datapoints length; corresponding to 20.48 s), and estimated the strength of generalized synchronization for all 210 non-redundant combinations of inter- and intrahemispheric sensoring electrode contacts.

B. Measuring Nonlinear Interdependencies

The state spaces of dynamical systems V and W can be reconstructed from time series of their observables using the method of time-delay embedding [6]. With an embedding dimension m and time delay d delay vectors read:

$$\begin{aligned} \mathbf{v}_n &= (v_n, \ldots, v_{n-(m-1)d}),\ n = 1, \ldots, K \\ \mathbf{w}_n &= (w_n, \ldots, w_{n-(m-1)d}),\ n = 1, \ldots, K. \end{aligned} \tag{1}$$

K is the number of data points. Let $r_{n,j}$ and $s_{n,j}$, $j = 1, \ldots, k$, denote the time indices of the k nearest neighbors of $\mathbf{v}_n$ and $\mathbf{w}_n$, respectively. For each $\mathbf{v}_n$, the mean squared Euclidean distance to its k neighbors is denoted by:

$$R_n^{(k)}(V) = \frac{1}{k} \sum_{j=1}^{k} (\mathbf{v}_n - \mathbf{v}_{r_{n,j}})^2 \tag{2}$$

The *W-conditioned* mean squared Euclidean distance can be derived by replacing the nearest neighbors by the equal time partners of the closest neighbors of $\mathbf{w}_n$:

$$R_n^{(k)}(V|W) = \frac{1}{k} \sum_{j=1}^{k} (\mathbf{v}_n - \mathbf{v}_{s_{n,j}})^2 \tag{3}$$

Following Refs. [7], [21] we define the nonlinear interdependence measure N as:

$$N^{(k)}(V|W) = \frac{1}{K} \sum_{n=1}^{K} \frac{R_n(V) - R_n^{(k)}(V|W)}{R_n(V)} \tag{4}$$

where the mean distance of $\mathbf{v}_n$ to all other vectors in state space is used for normalization:

$$R_n(V) = \frac{1}{K-1} \sum_{j \neq n} (\mathbf{v}_n - \mathbf{v}_j)^2 \tag{5}$$

Low values of $N^{(k)}(V|W)$ indicate independent systems (also slightly negative values are possible), while $N^{(k)}(V|W) \to 1$ for identical systems. The opposite interdependence $N^{(k)}(W|V)$ is defined in complete analogy and is in general not equal to $N^{(k)}(V|W)$. We here concentrate on the strength of generalized synchronization, which we define as:

$$N_s^{(k)} = \frac{N^{(k)}(V|W) + N^{(k)}(W|V)}{2} \tag{6}$$

Following Ref. [20], we reconstructed the state spaces with an embedding dimension $m = 10$ and a time delay $d = 5$ and calculated $N_s^{(6)}$ with $k = 6$ nearest neighbors. In the following we omit the superscript (k).

C. Estimating The Strength Of Generalized Synchronization With CNN

The CNN-based estimation of N_s has been described in detail elsewhere [19], [20]. Briefly, we performed all simulations on a software CNN (cf. [22]) implemented within our distributed computing system [23]. We consider a homogeneous two dimensional lattice of $M_x = M_y = 64$ cells, and the state equation for cell (i, j) reads:

$$\begin{aligned} \frac{d}{d\tau} \kappa_{i,j}(\tau) = &-\kappa_{i,j}(\tau) + \sum_{k,l \in \mathcal{U}_A} A_{k,l}(\mu_{i-k,j-l}(\tau)) \\ &+ \sum_{k,l \in \mathcal{U}_B} B_{k,l}(\eta_{i-k,j-l}) + Z \end{aligned} \tag{7}$$

where $\kappa_{i,j}(\tau)$ denotes the state variable of cell (i, j), $\eta_{k,l}$ is the input of cell (k, l), and Z denotes a global cell bias. The output $\mu_{k,l}(\tau)$ of cell (k, l) is determined by a sigmoidal output function. We used polynomial-type feedback and feedforward template functions $A_{k,l}$ and $B_{k,l}$ of order 3 and restricted ourselves to a minimum possible 3×3 sphere of influence $(k, l \in \mathcal{U}_{A,B})$.

For EEG analysis we linearly mapped the normalized (zero mean, unit variance) EEG time series (K=4096 datapoints) to the co-domain of the CNN cells $[-1, 1]$. Given EEG time series $(v(n), w(n), n = 1, \ldots, K)$ from two electrode contacts, we assigned $v(n)$ to the input $\eta_{k,l}$ and $w(n)$ to the initial state $\kappa_{i,j}(0)$ using a linewise alignment of the data. The *closed spiral* boundary condition, where all boundary cells are connected to the cells on the opposed side with an offset of 1 for each row, preserves the chronological sequence of the time series. For numerical integration of Eq. (7) we used Euler's integration method with a step size of 0.2 and 200 integration steps resulting in a transient time of τ_{trans}=40.

In order to derive a CNN-based estimate of the strength of generalized synchronization, we define:

$$N_s^{\text{CNN}} = \left(\frac{N_s^{\max} - N_s^{\min}}{M_x M_y} \sum_{m=0}^{M_x M_y - 1} \frac{\mu_m(\tau_{\text{trans}}) + 1}{2} \right) + N_s^{\min} \tag{8}$$

where $N_s^{\min}$ and $N_s^{\max}$ can be chosen either as 0 and 1 or as >0 and <1, respectively, depending on the specific application.

For network optimization we performed an *in-sample optimization* with data from a single patient (patient #1) only.

Moreover, we restricted ourselves to recordings from an electrode combination that showed best seizure prediction performance in previous studies [13]. We compiled a training set that consisted of $L = 16$ randomly selected pairs of EEG segments (K=4096 datapoints; 5 min. EEG recording) together with the respective calculated nonlinear interdependency values N_s (cf. Eq. (6)). One half of EEG segments showed high synchronization values ($N_s \in [0.84, 0.86]$), the other half exhibited low synchronization values ($N_s \in [0.29, 0.31]$). We adjusted $N_s^{\min}$ and $N_s^{\max}$ to this range of values of N_s. The desired output was defined as $\mu^{\mathrm{Ref}} = +1$ for segments with high N_s and as $\mu^{\mathrm{Ref}} = -1$ for segments with low N_s.

After choosing random initial values for the templates A and B and for the global cell bias Z we iteratively minimized the cost function

$$\Gamma = \frac{1}{L}\sum_{l=0}^{L-1}\left(\frac{1}{4M_xM_y}\sum_{m=0}^{M_xM_y-1}(\mu_{m,l}(\tau_{\mathrm{trans}}) - \mu_l^{\mathrm{Ref}})^2\right) \tag{9}$$

in order to find optimal CNN parameters (evolutionary optimization algorithm; population size: 50; survivors: 10; immigrants per generation: 10; iteration steps: 30000; cf. [24], [25], [26]).

In order to quantify the approximation accuracy in out-of-sample investigations (see. Sect. III) we consider the normalized absolute deviation

$$\delta = \frac{1}{L_w}\sum_{i=0}^{L_w-1}\left|N_s^{\mathrm{CNN}}(i) - N_s(i)\right| \tag{10}$$

of the approximated from the calculated temporal evolution of the strength of generalized synchronization, where L_w denotes the number of EEG segments. The profiles of our characterizing measures – that were obtained from recorded EEG data – usually contain fluctuations and therefore in principle have a non-zero probability of attaining any course within their range of definition. We thus aimed at rejecting the null hypothesis of the temporal evolution of N_s^{CNN} being a random process. Following the concept of surrogate time series [27], we generated (for each profile under investigation) 19 random sequences (values confined to $[-1, 1]$), and after applying Eq. (8) we calculated δ for each random sequence. Only if δ for the original synchronization profile exceeds the distribution of values for the random sequences the null hypothesis can be rejected (one-sided rank-order test with $\alpha = 5\%$).

III. Results

A. Intraindividual Generalization Properties

As mentioned already above we optimized our CNN using about 5 minutes of EEG data recorded from a selected combination of electrode contacts in one patient (patient #1). For this particular patient and combination of electrodes our CNN allowed to reproduce – in an out-of-sample validation – the temporal evolution of the strength of synchronization over a period of almost five days with an accuracy of $\delta = 0.09$ (cf. [19], [20]). For the remaining 219 combinations of electrodes we obtained a similar accuracy (cf. Table I), and we could reject the null hypothesis of a random sequence for more than 50 % of combinations of electrodes.

Pat. Id.	Recording time [h]	$\bar{\delta}$	$\delta_{\max}$	$\delta_{\min}$	ΔE
#1	107	0.08	0.31	0.01	52%
#2	173	0.29	0.46	0.01	7%
#3	195	0.17	0.36	0.01	61%
#4	142	0.12	0.28	0.01	64%
#5	152	0.11	0.18	0.01	66%
#6	188	0.14	0.23	0.01	85%
#7	257	0.11	0.18	0.01	60%
#8	137	0.12	0.19	0.01	11%
#9	154	0.14	0.36	0.01	48%
#10	153	0.15	0.26	0.02	23%

TABLE I

Results of within- and across-subject out-of-sample validation. $\bar{\delta}$ quantifies the mean approximation accuracy over all 210 electrode combinations, and $\delta_{\max}$ and $\delta_{\min}$ denote the worst and best approximation accuracy. ΔE denotes the fraction of electrode combinations for which the null hypothesis of a random sequence could be rejected. Small sections of EEG data from patient #1 were used for in-sample optimization.

B. Interindividual Generalization Properties

In another out-of-sample validation we used the CNN optimized for patient #1 (see above) and approximated the synchronization profiles for the EEG data from the other nine patients without further adjustments. Again this was carried out for all 210 electrode combinations in each patient. Our findings are summarized in Table I.

The approximation accuracy ranged between 0.11 and 0.29, and in six out of nine patients we could reject the null hypothesis of a random sequence for at least half of the number of electrode combinations.

IV. Conclusions

We have investigated generalization properties of a CNN-based approximation of the strength of generalized synchronization between EEG time series recorded in different areas of the human epileptic brain. We optimized our CNN using about 5 minutes EEG from a single patient and a single combination of sensoring electrodes, and subsequently used the CNN to approximate multichannel synchronization profiles, lasting days, from a group of nine patients suffering from temporal lobe epilepsy. Findings obtained from an intraindividual and interindividual out-of-sample validation indicate that our CNN is able to extract relevant information about spatial-temporal neuronal synchronization processes in different human epileptic brains. Although further improvements could be gained by a patient-specific adjustment of CNN templates, it can be

expected that the already achieved approximation accuracy paves the way for seizure prediction studies in a larger group of patients using our CNN-based approximation of neuronal synchronization. The detection of preseizure states at a sensitivity and specificity acceptable for clinical implementation would render CNN highly attractive for the development of miniaturized seizure prediction devices.

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REFERENCES

[1] A. S. Pikovsky, M. G. Rosenblum, and J. Kurths, *Synchronization – A universal concept in nonlinear sciences*. Cambridge, UK: Cambridge University Press, 2001.

[2] S. Boccaletti, J. Kurths, G. Osipov, D. L. Valladare, and C. S. Zhou, "The synchronization of chaotic systems," *Phys. Rep.*, vol. 366, pp. 1–101, 2002.

[3] H. Fujisaka and T. Yamada, "Stability theory of synchronized motion in coupled dynamical systems," *Prog. Theor. Phys.*, vol. 69, pp. 32–47, 1983.

[4] V. S. Afraimovich, N. N. Verichev, and M. I. Ravinovich, "General synchronization," *Izv. VUZ. Radiophiz.*, vol. 29, p. 795, 1986.

[5] H. D. I. Abarbanel, N. Rulkov, and M. Sushchik, "Generalized synchronization of chaos: The auxiliary system approach," *Phys. Rev. E*, vol. 53, pp. 4528–4535, May 1996.

[6] F. Takens, "Detecting strange attractors in turbulence," in *Dynamical Systems and Turbulence*, ser. Lecture Notes in Mathematics, D. A. Rand and L. S. Young, Eds. Berlin: Springer-Verlag, 1980, vol. 898, pp. 366–381.

[7] J. Arnhold, P. Grassberger, K. Lehnertz, and C. E. Elger, "A robust method for detecting interdependences: application to intracranially recorded EEG," *Physica D*, vol. 134, pp. 419–430, 1999.

[8] C. E. Elger, F. Mormann, T. Kreuz, R. G. Andrzejak, C. Rieke, R. Sowa, S. Florin, P. David, and K. Lehnertz, "Characterizing the spatio-temporal dynamics of the epileptogenic process with nonlinear EEG analysis," in *Proceedings of the 7th IEEE International Workshop on Cellular Neural Networks and their Applications*, R. Tetzlaff, Ed. Singapore: World Scientific, 2002, pp. 228–242.

[9] F. Mormann, C. E. Elger, and K. Lehnertz, "Seizure anticipation: from algorithms to clinical practice," *Curr. Opin. Neurol.*, vol. 19, pp. 187–193, 2006.

[10] F. Mormann, R. G.Andrzejak, C. E. Elger, and K. Lehnertz, "Seizure prediction: the long and winding road," *Brain*, vol. 130, pp. 314–333, 2007.

[11] K. Lehnertz, F. Mormann, H. Osterhage, A. Müller, A. Chernihovskyi, M. Staniek, J. Prusseit, D. Krug, S. Bialonski, and C. E. Elger, "State-of-the-art of seizure prediction," *J. Clin. Neurophysiol.*, vol. 24, p. 147, 2007.

[12] K. Lehnertz, M. Le Van Quyen, and B. Litt, "Seizure prediction," in *Epilepsy: A Comprehensive Textbook, 2nd ed.*, J. J. Engel and T. A. Pedley, Eds. Philadelphia: Lippincott, Williams & Wilkins, 2007, p. 1011.

[13] F. Mormann, T. Kreuz, C. Rieke, R. G. Andrzejak, A. Kraskov, P. David, C. E. Elger, and K. Lehnertz, "On the predictability of epileptic seizures," *Clin. Neurophysiol.*, vol. 116, pp. 569–587, 2005.

[14] M. Le Van Quyen, J. Soss, V. Navarro, R. Robertson, M. Chavez, M. Baulac, and J. Martinerie, "Preictal state identification by synchronization changes in long-term intracranial EEG recordings," *Clin. Neurophysiol.*, vol. 116, pp. 559–568, 2005.

[15] B. Schelter, M. Winterhalder, T. Maiwald, A. Brandt, A. Schad, A. Schulze-Bonhage, and J. Timmer, "Testing statistical significance of multivariate time series analysis techniques for epileptic seizure prediction," *Chaos*, vol. 16, p. 013108, 2006.

[16] H. Osterhage, F. Mormann, M. Staniek, and K. Lehnertz, "Measuring synchronization in the epileptic brain: a comparison of different approaches," *Int. J. Bifurcation Chaos*, vol. 17, pp. 3539–3544, 2007.

[17] R. Sowa, F. Mormann, A. Chernihovskyi, S. Florin, C. Elger, and K. Lehnertz, "Estimating synchronization in brain electrical activity from epilepsy patients with cellular neuronal networks," in *Proc. 8th IEEE International Workshop on Cellular Neural Networks and their Applications*, T. Roska, M. Gilli, B. Shi, and A. Zarandy, Eds. Budapest: Amulett'98 Kft., 2004, pp. 327–332.

[18] R. Sowa, A. Chernihovskyi, F. Mormann, and K. Lehnertz, "Estimating phase synchronization in dynamical systems using cellular nonlinear networks," *Phys. Rev. E*, vol. 71, p. 061926, 2005.

[19] D. Krug, H. Osterhage, C. E. Elger, and K. Lehnertz, "Estimating generalized synchronization in brain electrical activity from epilepsy patients with cellular nonlinear networks," in *Proc. 10th IEEE International Workshop on Cellular Neural Networks and their Applications*, V. Tavsanoglu and S. Arik, Eds. Piscataway, NJ: IEEE Press, 2006, pp. 68–72.

[20] ——, "Estimating nonlinear interdependences in dynamical systems using cellular nonlinear networks," *Phys. Rev. E*, vol. 76, p. 041916, 2007.

[21] R. Quian Quiroga, A. Kraskov, T. Kreuz, and P. Grassberger, "Performance of different synchronization measures in real data: A case study on electroencephalographic signals," *Phys. Rev. E*, vol. 65, p. 041903, 2002.

[22] R. Kunz, R. Tetzlaff, and D. Wolf, "Brain electrical activity in epilepsy: Characterization of the spatio-temporal dynamics with cellular neural networks based on a correlation dimension analysis," in *Proceedings of the IEEE International Symposium on Circuits and Systems*, J. Vandevalle and M. Hassler, Eds. Piscataway, NJ: IEEE Press, 2000, pp. 1024–1027.

[23] A. Müller, H. Osterhage, R. Sowa, R. G. Andrzejak, F. Mormann, and K. Lehnertz, "A distributed computing system for multivariate time series analyses of multichannel neurophysiological data," *J. Neurosci. Meth.*, vol. 152, pp. 190–201, 2006.

[24] J. H. Holland, *Adaptation in natural and artificial systems*. Ann Arbor, USA: The University of Michigan Press, 1975.

[25] T. Kozek, T. Roska, and L. O. Chua, "Genetic algorithm for CNN template learning," *IEEE Trans. Circ. Syst.*, vol. 40, pp. 392–402, 1993.

[26] R. Kunz and R. Tetzlaff, in *Proceedings of the 6th IEEE International Workshop on Cellular Neural Networks and Their Applications*, L. Fortuna, Ed. Piscataway, NJ: IEEE Press, 2000, pp. 241–246.

[27] T. Schreiber and A. Schmitz, "Surrogate time series," *Physica D*, vol. 142, p. 346, 2000.