Evaluation of non-linear properties of epileptic activity using largest Lyapunov exponent

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ABSTRACT

Absence seizures are known to be highly non-linear large amplitude oscillations with a well pronounced main time scale. Whilst the appearence of the main frequency is usually considered as a transition from noisy complex dynamics of baseline EEG to more regular absence activity, the dynamical properties of this type of epileptiformic activity in genetic absence animal models was not studied precisely.

Here, the estimation of the largest Lyapunov exponent from intracranial EEGs of 10 WAG/Rij rats (genetic model of absence epilepsy) was performed. Fragments of 10 seizures and 10 episodes of inter-ictal on-going EEG each of 4 s length were used for each animal, 3 cortical and 2 thalamic channels were analysed. The method adapted for short noisy data was implemented. Positive values of the largest Lyapunov exponent were found for baseline as well as for spike wave discharges (SWDs), with values for SWDs being significantly less than for inter-ictal baseline on-going activity.

Current findings may indicate that on-going inter-ictal EEG and SWD are both chaotic processes. Also, the SWD activity was shown to be less chaotic than the baseline one.

Keywords: absence epilepsy, largest Lyapunov exponent, time series analysis, EEGs, spike-wave discharges, WAG/Rij rats

1. INTRODUCTION

Investigation of brain activity using different approaches of non-linear dynamics became very popular in recent years. The first studies of various biological rhythms using these tools[1] showed that processes in the brain are normally characterised by the presence of irregular components with a high degree of complexity. Such a dynamics gives many functional advantages, since chaotic systems are capable of operating over a wide range of conditions, and thus easy to adapt to changes.

However, clearly expressed periodicity appears in many pathological states and ageing is accompanied by a decrease in the degree of chaos and complexity.[2] Therefore, estimating measures like Lyapunov exponents, fractal dimension, and synchronisation indices from experimental data are very important in electroencephalographic studies,[3,4] because electroencephalography is currently the most affordable and widely used method to study brain activity. A large number of researchers carried out EEG studies, developing and applying methods of non-linear dynamics in the last decade.[5–9]

Absence epilepsy is a generalised form of epilepsy with a focal cortical origin that is widespread among children and co-called adolescents (humans under 14 years of age) and it usually manifests as a short-term (typically 3–30 s) decrease in responsiveness and consciousness. An absence discharge is not difficult to detect visually from the EEG: it is characterised by typical large amplitude 3 Hz oscillations in the form of trains of sharp spikes and slow waves. Also it was mentioned multiple times that oscillations become more periodic comparably to baseline activity.[10,11] However, approaches considering the problem of coupling analysis used similar processing of preictal base-line data and epochs with epileptiformic activity.[12–14] Here, we propose to quantify the complexity and

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regularity of inter-ictal and ictal EEG signal evaluating the largest Lyapunov exponent: a positive value is an indicator of a chaotic regime, as was already mentioned once.[15]

In this work experimental EEG signals taken from WAG/Rij rats were considered. First, the theoretical basis of calculating the largest Lyapunov exponent from time series was given. Second, the experimental data were described and processed. Finally, the obtained results were discussed.

2. METHOD

The Lyapunov exponent characterises the behaviour of the two initially very close points in a phase space. The distance between them changes exponentially with time, just with the magnitude of the largest Lyapunov exponent Λ. Therefore, a zero value of Λ indicates the presence of a periodic regime, while a positive one means that the system is in a chaotic regime.

There are several methods to evaluate Lyapunov exponents from time series. One of them[16] focuses on a "fiducial" trajectory. This method was used previously to study the Lyapunov exponent from WAG/Rij rats.[15] A single nearest neighbour is repeatedly replaced when its separation from the reference trajectory grows beyond a certain limit. Additional computation is also required since phase space orientation should be preserved. Other methods[17,18] are based on the construction of local maps — forecasting models. These models map whole neighbourhood of small vectors of variance between to different but close trajectories into a succeeding neighbourhood of evolved vectors.

In the current study the method proposed in[19] was used. This method is fast and easy to implement, since it uses a simple measure of exponential divergence, so it is not necessary to approximate the tangent map. Furthermore, it is more accurate for small data sets because it takes into account all the available data, so the averaging over the attractor is sufficiently better than for approaches which only analyse a single fiducial trajectory. Its main shortcoming is that only the largest Lyapunov exponent can be calculated.

The first step of the used approach is attractor reconstruction from a single time series. For this purpose the method of time delays[20] was used. The choice of the method parameters is very important to evaluate the largest Lyapunov exponent correctly, therefore we dwell upon it in detail.

2.1 METHOD OF DELAYS

Having recorded the dependency of observed variable on the time $x = x(t)$, one should define some time step τ and an integer d, and construct a d-dimensional vector which components are the values of x at time t, $t-\tau$, $t-2\tau$, …, $t-(d-1)\tau$, i. e.

$$\mathbf{x}(t) = \left(x(t), x(t-\tau), x(t-2\tau), \ldots, x(t-(d-1)\tau)\right). \tag{1}$$

The vector $x(t)$ defines a point in d-dimensional space, which moves along a trajectory over time t. In the discrete case the equation (1) has the form

$$\mathbf{x}_k = (x_k, x_{k-L}, x_{k-2L}, \ldots, x_{k-(d-1)L}), \tag{2}$$

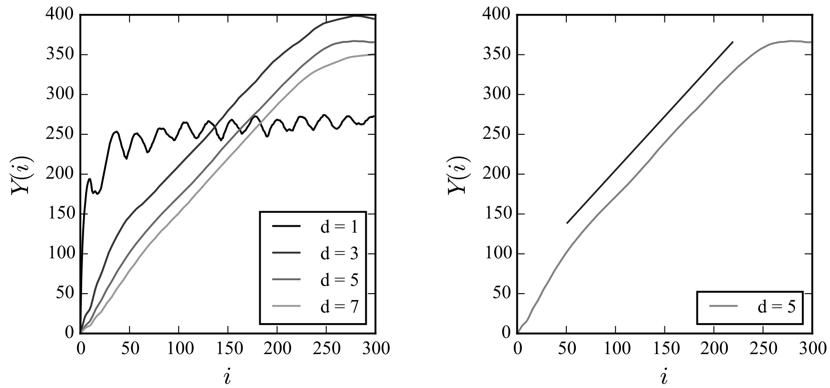
where L is lag (fixed integer, e. g., $1, 2, 3, \ldots$). Assuming that one is dealing with a steady-state behaviour of a dissipative system, the phase plot of an attractor is reconstructed.

It should be noted that the above mentioned is true only if lag τ (or in the discrete case lag L) is chosen properly. It has been shown that this value should be chosen equal to a quarter of the characteristic period[20] or, if this is not possible, equal to the first minimum of the mutual information function.[18]

Reconstructed by the method of delays, trajectory can be represented as a matrix $\hat{\mathbf{X}}$ in which each row is a state vector in a phase space.

$$\hat{\mathbf{X}} = (\mathbf{x}_1, \mathbf{x}_2, \ldots, \mathbf{x}_M), \tag{3}$$

where $\mathbf{x}_i$ is a state of the system at time moment i. For time series $x_1, x_2, \ldots, x_N$ each $\mathbf{x}_i = \big(x_i, x_{i-L}, \ldots, x_{i-(d-1)L}\big)$. Thus, $\hat{\mathbf{X}}$ is the $M \times d$ matrix, where $M = N - (d-1)L$.



(a) (b)

Figure 1. Typical dependencies of $\langle \ln(divergence) \rangle$ versus discrete time for the Lorenz attractor — (a) for different embedding dimensions d, — (b) with illustration of getting a correct slope from linear region.

2.2 LARGEST LYAPUNOV EXPONENT ESTIMATION

Given a reconstructed phase space, it is necessary to find the nearest neighbour for each point of the trajectory. Assuming that the nearest neighbour to point $\mathbf{x}_j$ is such $\mathbf{x}_n$, for which the distance (4) between them is minimal:

$$d_j(0) = \min_n \|\mathbf{x}_j - \mathbf{x}_n\|, \tag{4}$$

where $d_i(0)$ is the initial distance from point i to its nearest neighbour, and $\|\|$ is an Euclidean norm. In addition, it should be noted that the nearest neighbours should not be close to each other in time, e.g not closer than the value of the lag: $|j - n| > L$. This condition allows to consider each pair of nearest neighbours as an initial condition for pair of close but different trajectories.

Then the largest Lyapunov exponent can be estimated as a function of the average difference between the nearest neighbours. From the definition of the largest Lyapunov exponent i-th pair of the nearest neighbours diverge approximately at a rate given by Λ:

$$d_j(i) \approx d_j(0) e^{\Lambda i \Delta t}. \tag{5}$$

By taking the logarithm of both sides of (5), one obtains

$$ln\ d_j(i) \approx ln\ d_j(0) + \Lambda i \Delta t). \tag{6}$$

Equation 6 represents a set of approximately parallel lines, the slope of each is proportional to Λ. The largest Lyapunov exponent is estimated using the least squares routine to approximate the curve $y(i)$ with a line.

$$y(i) = \frac{1}{\Delta t} \left\langle ln\ d_j(i) \right\rangle_j \tag{7}$$

This process of averaging is the key to calculate accurate values of Λ, using small, noisy data sets. Note that in (6) the term $d_j(0)$ is responsible for normalisation, but since normalisation is not required to estimate only the largest Lyapunov exponent, in (7) this term is no longer included.

Dependencies $y(i)$ are evaluated for different embedding dimensions d (see Fig. 1(a)) and, if it is possible to find linear parallel sites for nearby dimension values (see Fig. 1(b)), the slope of the approximating line is an estimate of the largest Lyapunov exponent. This linear sites must not be located for very small values of i, since for these values the estimate is not guaranteed to represent the direction of the maximal increase of perturbation. Also, very high values of i are not appropriate since the perturbation does not grow exponentially any more.

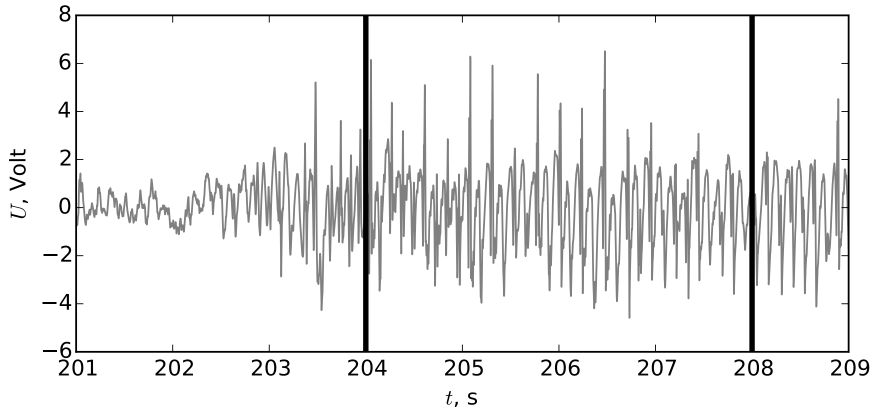


Figure 2. A fragment of the cortical layer 6 EEG signal with a Spike-wave discharge typical for an absence seizure. Vertical lines mark considered EEG parts.

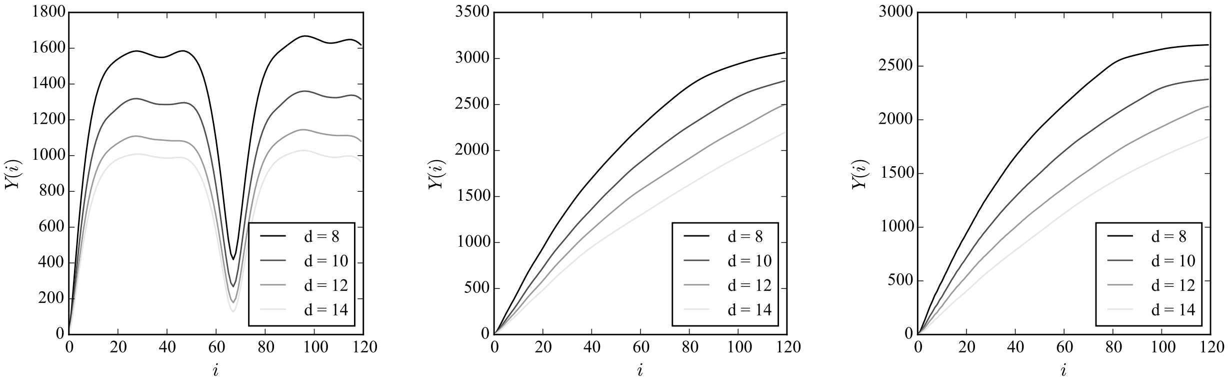
3. EXPERIMENTAL DATA PROCESSING

3.1 DATA DESCRIPTION

Data were obtained from a previously used and published data set[12] in which male WAG/Rij rats (6–9 months) were used as experimental subjects. The Ethical Committee on Animal Experimentation of Radboud University Nijmegen (RU-DEC) approved the experiment. EEGs were recorded with a self-constructed electrode system for multi-site EEG recording at specified and verified brain locations. Stainless steel electrodes insulated with poliamide, diameter: 127 μm were fixated in a Teflon block, which contained small holes located at the relative A/P & M/L coordinates of the multiple electrode target structures as determined by the rat brain atlas of Paxinos and Watson.[21] 12 electrodes wires including those from reference and ground were glued to the teflon-block and fixed at the top-site to a connector pin, which was entered into an electrode pedestal suitable for the connection to a multi-lead electrode cable, which was connected to a swivel allowing long term recording in freely moving and well-adapted rats. The EEG signals were amplified with a physiological amplifier (TD 90087, Radboud University Nijmegen, Electronic Research Group), filtered by a band pass filter with cut-off points at 1(HP) and 100(LP) and a 50 Hz Notch filter, and digitalised with a constant sample rate of 2048 Hz by WINDAQ-recording-system (DATAQ-Instruments). EEG of each rat was recorded for a period of 4 hours during the dark phase. In this work, records from from cortical layers 4, 5 and 6 of the perioral region of the somatosensory cortex and from two thalamic sites: the ventral-postero-medial thalamus and the posterior thalamic nucleus from 10 rats were used. Time series of 4 s length at the beginning of 10 spike-wave discharge (SWD) and of 10 periods of inter-ictal baseline activity were analysed for each rat.

3.2 OPTIMAL PARAMETERS SELECTION

It was shown considering etalon non-linear systems[19] that the efficiency of the described method is mainly determined by the embedding dimension d and the lag L. When one selects these parameters by the above-mentioned methods, the curve for evaluation of largest Lyapunov exponent will look like Fig. 1(a). However, processing experimental EEG signals showed that it does not happen (see Fig. 3(a)). It was found that a linear region (though not so long as for reference systems) of the curves can be achieved (see 2 b between $i = 60$ and $i = 100$ for $d = 5$), if lag is chosen in the following way. Let L' be a lag, which is used for reconstruction of the phase space, and L is used for nearest neighbour search. Then it is possible to achieve dependence $y(i)$ as illustrated in fig. 3(b), if L is equal to first minimum of mutual information, and L' is significantly smaller, e. g. $L' = \frac{L}{7}$. It can be explained by the fact that the signal has a number of independent time scales (and corresponding spectral components), some of them being much smaller than the main one. The consideration of these small time scales occurred to be crucial for efficiency of the method.



(a) (b) (c)

Figure 3. Typical dependencies of ln(*divergence*) versus discrete time for EEG signal during absence seizure: (a) with a conventional lag, (b) with a proposed lag, and during baseline activity — (c) with a proposed lag.

To examine the difference between absence and baseline activity the same procedure was applied to previously chosen[12] segments of baseline. Linear segment was more difficult to detect for some cases (see Fig. 3 c), so some segments (about 30%) were excluded. The variance of largest Lyapunov exponent estimates was usually larger for baseline periods. The possible reason for this fact is that the baseline activity is more complex (a larger dimension is necessary) and noisy due to a lower signal to noise ratio.

4. EXPERIMENTAL RESULTS

In total, we processed 500 four-second parts of EEG signals at the beginning of SWD onsets: 10 time series from each of the 10 selected rats from 5 channels for absence activity and from 6 to 10 series from each of the 10 selected rats from 5 channels for baseline activity. Estimates of the largest Lyapunov exponent were averaged first over all discharges for each rat separately, and then over all rats. The average values with SEMs were presented in Fig. 4. The average values of estimates for the largest Lyapunov exponent $\langle\Lambda\rangle$ and their standard errors of the mean $\sigma_{\langle\Lambda\rangle}$ for all considered channels are shown in Fig. 4. The achieved values do not vary a lot across different animals: SEMs are small in comparison with the absolute values.

The largest Lyapunov exponent values obtained for thalamus are usually larger than for the cortex. Using a two-way ANOVA followed by post-hoc tests it was shown that the $\langle\Lambda\rangle_{PO}$ and $\langle\Lambda\rangle_{VPM}$ differs both from $\langle\Lambda\rangle_{ctx4}$ and $\langle\Lambda\rangle_{ctx5}$ with p-value less than 0.05.

Comparing baseline and SWD activity one can notice that the mean values of Lyapunov exponent are significantly (based on a two-way ANOVA followed by post-hoc tests) less for SWDs than for the baseline activity. The difference was most clearly established for cortical layer 4: with p-value 10^{-4}, and for cortical layer 6: with p-value 0.002. For cortical layer 5 and both thalamic nuclei the difference was established with p-value 0.1.

The comparison of cortical layer 6 to others channels showed that the values in this channel were significantly less (with p-value 0.05) than in other channels as in baseline as during SWDs (except pair ctx4 and ctx6 during SWDs). It is an interesting finding, considering this layer is most likely to contain the focus for this type of epilepsy.

5. CONCLUSION AND DISCUSSION

The estimation of the largest Lyapunov exponent performed in this study indicates the presence of chaotic oscillations in the EEG signal during the absence discharge as well as during the baseline. The achieved results may show the complexity of the absence activity. However, the values of Lyapunov exponent estimated for the baseline activity were significantly higher than for the absence one. The results (especially the exact values) must be considered very preliminary since it was often mentioned that even for low dimensional oscillators results can

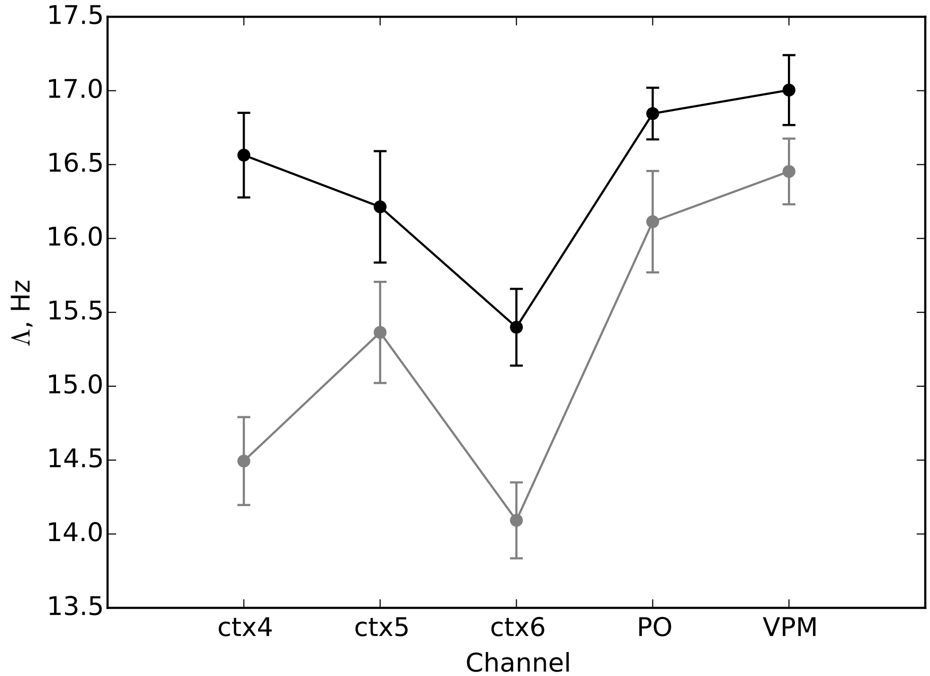


Figure 4. The estimates of the largest Lyapunov exponent for different channels for baseline activity (black) and SWDs (grey) averaged over all 10 rats with standard errors of the mean (SEMs).

be crucially contaminated by noise.[22,23] The absolute values achieved in this work were in 4–10 times higher than those obtained earlier.[15] This variation can be partly the result of different brain structures analysed and other method applied, as well as due to different electrode position and therefore unequal noise level. However, it is remarkable that the values obtained by us are not dramatically large in correspondence to the values known for many reference systems.[24] If a renormalisation of the time to the same frequency of the main timescale is performed, e. g. the values are only twice larger than for Lorenz system.

In sum, a special approach, adapted to specifics of the experimental data, is necessary to make more reliable estimations. One has to notice that, even if the chaotic nature of the absence discharges will be confirmed, this fact would not contradict to the well known fact that the absence activity is characterised by "regular" oscillations. Here, the interpretation of the term "regular" is important. A lot of reference systems of non-linear dynamics[25–28] can demonstrate chaotic oscillations which are characterised both by a positive (and sometimes very high[29]) values of the largest Lyapunov exponent and a single well established timescale, presence of which can be considered as a manifestation of regularity. Also the baseline activity was found to be more complex than the activity during SWD, since even the estimation of the largest Lyapunov exponent for baseline EEG turned out to be unsafe in some cases.

The main outcome of finding the chaotic nature of absence activity lays in a filed of empirical model construction. Such models are used for coupling analysis[30] or for automatic seizure detection.[31] And the signal properties were shown to be of great importance to succeed with these models.[24]

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