Delayed Mutual Information to Develop Functional Analysis on Epileptic Signals

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Abstract: Epilepsy is the second most prevalent brain disorder affecting approximately 70 million people worldwide. A modern approach to develop the brain study is to model it as a system of systems, represented by a network of oscillators, in which the emergent property of synchronisation occurs. Based on this perspective, epileptic seizures can be understood as a process of hyper-synchronisation between brain areas. To investigate such process, a case study was conducted applying Delayed Mutual Information (DMI) to perform functional connectivity analysis, investigating the channel capacity (C) and transmission rate (R) between brain areas — cortex, hippocampus and thalamus — during basal and infusion intervals, before the beginning of generalised tonic-clonic behaviour (TCG). The main contribution of this paper is the study of channel capacity and transmission rate between brain areas. A case study performed using 5 LFP signals from rodents showed that the applied methodology represents an another appropriate alternative to existing methods for functional analysis such as Granger Causality, Partial Directed Coherence, Transfer Entropy, providing insights on epileptic brain communication.

1 INTRODUCTION

Epilepsy is the second most common neurological disease (Organization et al., 2017) and affects approximately 70 million people worldwide (Spiciarich et al., 2019) representing a public health concern (Niriayo et al., 2019). It is a chronic disease of the central nervous system (CNS) that reaches people of all ages in which it is commonly associated with social difficulties (Beghi, 2019) and can cause health loss such as premature mortality and residual disability (Beghi et al., 2019).

Epilepsy-based studies usually uses electroencephalography (EEG) (Ibrahim et al., 2019) or local field potentials (LFP) (Biasiucci et al., 2019) to check brain electrical activity, although the use of electrodes directly in brain tissue is an important option to map electrical activity of the brain with better spatial resolution (Bartolomei et al., 2017).

The latest approach to study epilepsy is the analysis of hyper-synchronisation of brain frequencies oscillations as a feature (Yu et al., 2019). (Olamat and Akan, 2017) performed a nonlinear synchronisation analysis in LFP epileptic data introducing this new perspective. (Weiss et al., 2019) used the concept to understand seizure genesis and spreading in human limbic areas and (Devinsky et al., 2018) reported hyper-synchronisation to discuss epilepsy epidemiology and pathophysiology. The brain is modelled as a complex system where each region represents a subsystem and synchronization is an emergent property (Andrea Avena-Koenigsberger, 2017). Changes in this feature during the occurrence of epileptic seizures are an important aspect to understand the epileptic brain network and synchronization (Mei et al., 2019). The pathologic hyper-synchronisation of frequencies oscillations give rise to seizures (Berglind et al., 2018).

There is a hypothesis that high-frequencies oscillations are related with the cortical local brain in-

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formation processing whereas low-frequencies have connection with larger cortical networks (Anastasiadou et al., 2019). Consequently, the brain interactions through these areas can become complex because of interactions between oscillations at different frequency bands (Anastasiadou et al., 2019). In this situation, functional connectivity may be performed to detect dependencies among neurophysiological signals (Andrea Avena-Koenigsberger, 2017). It can be assessed through different methods with the aim to infer patterns of direct influences (Andrea Avena-Koenigsberger, 2017).

To estimate the dependency between time series there are several methods (Gribkova et al., 2018) and Mutual Information is one of them. It is an Information Theoretic and nonparametric approach that measures generalized, both linear and nonlinear, interdependence between two variables (Akbarian and Erfanian, 2017). This meets the accepted vision that real world time series usually are nonlinear and non stationary (Wan and Xu, 2018).

Usually, the Information Theoretic approaches do not make any hypothesis about the dependency between time series (Nichols et al., 2005). The use of time Delayed Mutual Information (DMI) seeks to quantify the information shared between time series taking into account the previous information content as function of time (Endo et al., 2015). (Li et al., 2018) demonstrated that DMI is a suitable option to develop analysis of nonlinear systems as in the case of neuroscience data. (Kim et al., 2018) used DMI to analyse information transmission of an EEG set from groups of people with mild Alzheimer disease. (Li et al., 2017) applied DMI to characterise hippocampal theta-driving neurons. (Chapeton et al., 2017) performed a study using intracranial EEG to identify effective connections in the brain that exhibit consistent timing across multiple temporal scales.

The objective of this paper is, in performing a case study using Delayed Mutual Information, to develop functional connectivity analysis in rodents LFP signals, investigating the channel capacity (C) and the transmission rate between brain areas. In addition, Surrogate method is used to evaluate the DMI measures. In section 2, it is presented the theory related to DMI and Surrogate. Section 3 describes the LFP data used and the applied methodology. Section 4 presents the achieved results, and in Section 5 the results are discussed. Finally Section 6 brings forward paper conclusions.

2 THEORY

This section presents the main theory required to develop this paper. First it is introduced Mutual Information explaining the main concepts of channel capacity and transmission rate. Then the Surrogate method, used to assess statistical significance of the performed analysis, is defined.

2.1 Delayed Mutual Information

The measure of how deterministic is a given variable can be determined through its entropy (H), defined by (Cover and Thomas, 2012):

$$H(X) = -\sum_{x\in\chi} p(x) log_a p(x) \tag{1}$$

where X is a discrete random variable, $p(x) = P\{X = x\}$ is the probability of X equal to x, $x \in \chi$, i.e. the probability mass function of X, and a is the logarithm base that provides the entropy measure in bits in the case of $a = 2$. Given a signal X and another signal Y, the Mutual Information may quantify the information shared between this signals, which means how much it is possible to reduce the uncertainty of signal X given the knowledge of signal Y (Cover and Thomas, 2012).

The Delayed Mutual Information (DMI) according to (Nichols et al., 2005) is the quantification of information shared between X and Y^τ where Y^τ is the signal displaced by a lag τ. It is mathematically defined as:

$$I(X;Y^\tau) = \sum_{x_n\in\chi}\sum_{y^\tau\in\gamma} p(x_n, y_{y-\tau}) log_a \frac{p(x_n, y_{n-\tau})}{p(x_n)p(y_{n-\tau})} \tag{2}$$

According to (Cover and Thomas, 2012) the channel capacity (C) represents the maximum measure of Mutual Information:

$$C = maxI(X,Y) \tag{3}$$

and according to (Proakis and Salehi, 2001) the channel capacity for DMI is quantified by its peak value. Also according to (Proakis and Salehi, 2001), the transmission rate estimation (R) can be written as a function of channel capacity and signal bandwidth (BW) in Hertz:

$$R = 2.BW.C \tag{4}$$

If the entropy is measured in bits, the transmission rate is going to be measured as bits/s.

2.2 Surrogate for Hypothesis Test

The investigation of information sharing between brain regions sometimes require the assertion of statistical significance for confidence in the functional analysis performed. In this case Surrogate may be useful (Lancaster et al., 2018).

One of the techniques to apply this method is the IAAFT technique, proposed by (Schreiber and Schmitz, 1996). It consists of generating a surrogate data from the original signal, keeping the same power spectrum and randomizing Fourier phases, creating uncorrelated signals. Applying DMI on surrogate data represents the measures that are expected when signals do not share any connectivity. Therefore, when comparing the statistics from original signals and the surrogate data statistics, the null hypothesis can be accepted or rejected. Some literature can be reviewed in neuroscience related to the use of Surrogate to assist the type of interdependency among electroencephalographic signals (Pereda et al., 2005; Faes et al., 2010; Subramaniyam and Hyttinen, 2015; Adkinson et al., 2019).

Related with the number of surrogate data to be created, there is a well established rank-order test, proposed by (Theiler et al., 1992), that can be used (Schreiber and Schmitz, 2000). First, assume Ψ is the probability of false rejection, then, define the level of significance (S) as:

$$S = (1 - \Psi) \cdot 100\% \tag{5}$$

The number of surrogate data to be created (M) is defined as follows:

$$M = \frac{K}{\Psi} - 1 \tag{6}$$

where K is an integer number defined by the type of test - 1 if it is one-sided and 2 in the case of a two-sided test. Usually, $K = 1$ is adopted due to computational effort to generate surrogates (Schreiber and Schmitz, 2000).

3 METHODOLOGY

The section details the methodology used to analyse the local field potential signals, in order to assess mutual information, channel capacity and transmission rate between brain areas. Furthermore, it describes the methodology employed to acquire the LFP signals and the computational environment.

3.1 Applied Methodology

The diagram presented in Figure 1 depicts the applied methodology. The first step — blue box in Figure 1 — is to calculate the LFP signals entropy for cortex (Cx), hippocampus (Hp) and thalamus (Th).

Then, in the second step, the optimal number of bins to apply Mutual Information is determined — orange box in Figure 1 — as follows: The rodents LFP signals are discretized with different number of bins — 2, 4, 8, 16, 32, 64 and 128 where used — and DMI is applied among brain areas. Next, the DMI measures are compared to find the best number of bins - the DMI curve for a given number of bins that is closest to highest DMI curve. Figure 2 explain better the method. Another important measure performed is the Kolmogorov-Smirnov test to compare the group of rodents to check if there is a statistical difference between groups.

The third step is to apply Delayed Mutual Information to understand the information sharing and depict the lag where there the maximum value occurs, therefore determining the channel capacity. In the fourth step, surrogate data is created with Iterative Amplitude Adjusted Fourier Transform (IAAFT) algorithm for cortex, hippocampus and thalamus signals. In this case study, 35 signals for 97% significance level were generated. In the fifth step, each surrogate is combined with other two original signals to perform DMI analysis, investigating the connectivity significance between brain areas.

The surrogate data is compared with the original DMI measures by means of Kolmogorov-Smirnov (KS) test. In this paper, p-value = 5% was chosen to evaluate the maximum mutual information and its values. The last step is to apply Fast Fourier Transform to verify the signal's bandwidth and, finally, calculate the transmission rate between brain areas.

The applied methodology described was used to investigate two periods of LFP signals: basal and convulsant drug infusion, until generalized tonic-clonic (TCG) behaviour. The analysis was performed in the recordings of five rats.

Simulations were developed in Python language, using the packages: Matplotlib, Nolitsa, Numpy, Pandas, Scipy, Seaborn and Time. The code was executed on a computer with an Intel i7 processor, 8GB of RAM, running MAC OS 10.14.6 operational system.

3.2 Database for Case Study

We used LFP signals database from Interventional Laboratory of Neuroengineering and Neuroscience

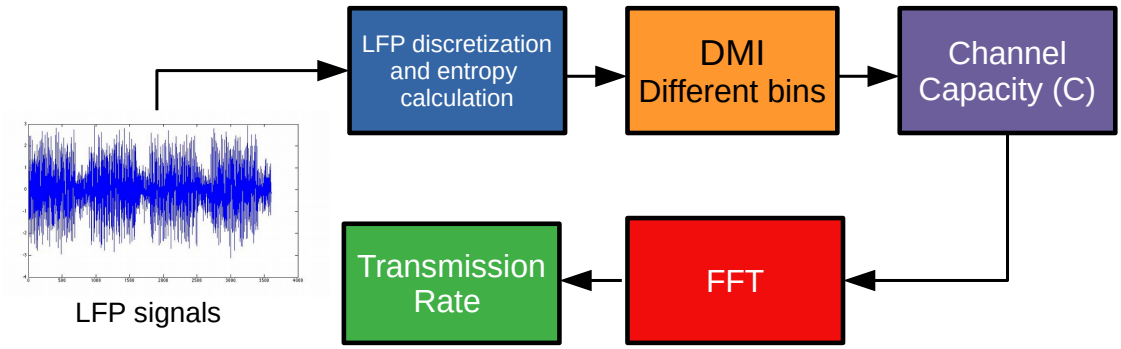

Figure 1: Summary of applied methodology: First, the LFP signals are discretized and their entropy are calculated. Then, DMI with different bin sizes are computed to determine the value that best fits the dataset. After the optimal number of bins is identified, DMI is calculated among all rodent brain signals (Cx, Hp and Th) and channel capacities are determined. To calculate the transmission rate between brain areas, Fast Fourier Transform (FFT) is applied to all LFP signals to check the signal's bandwidth. Finally, the channel capacity and signal's bandwidth are used to find the transmission rate between brain areas.

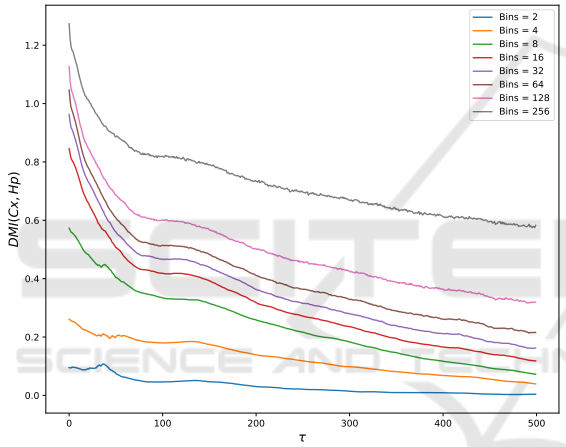

Figure 2: Delayed Mutual Information performed with different number of bins between two brain areas (τ is given in samples). As can be observed the highest curve is presented for 256 bins. In this case the better resolution for DMI is 256 bins. However, if the 256 bins curve would not exist, only the other curves, it is possible to check three curves with almost same values (32, 64 and 128 bins). In that case it could be possible to choose 32 bits to perform analysis because the results are similar to 128 bins curve and the computational processing would be smaller.

(LINNce) from Federal University of São João Del Rei. The laboratory employs male Wistar rats weighing between 250 and 350 grams coming from the University Central Biotherm to acquire data and evaluate methods of electrical stimulation. All described procedures are in according to ethics committee under-protocol 31/2014.

The signal recording is conducted with the aid of electrodes (monopolar type and stainless steel covered by teflon) placed directly inside the right thalamus and hippocampus of the rat's brain through stereotactic surgery (Cota et al., 2016). In addition, two microsurgical screws were implanted (length 4.7 mm, diameter 1.17 mm, Fine Science Tools, Inc., North Vancouver, Canada) aiming the cortical registration of right hemisphere and to operate as reference in frontal bone. The electrodes and screws were positioned with assistance of neuroanatomic atlas (Paxinos and Watson, 2013).

The LFP signals for each rodent was registered while the subject was simultaneously filmed, to perform behavioural analysis (observe classic seizure features such as facial automatisms, myoclonic concussion, head myoclonus, anterior and posterior limbs myoclonus, elevation and fall, generalized tonic-clonic seizure) to allow their correlation with the electrophysiological events observed during LFP recording. For all rodents the time of recording was the same with ten minutes of duration.

LFP recording was performed using 1 kHz sampling rate. Signals were amplified 2000 V/V through A-M Systems (model 3500) amplification system and digitalized on National Instruments (PCI 6023E) A/D converter controlled by developed LINNce Virtual Instrument from LabView platform. Sequentially, they were filtered using a second-order Butterworth filter (0.3 to 300 Hz band).The power grid noise at 60 Hz frequency was mitigated with use of shielded cables and Faraday cage.

4 RESULTS

During basal and infusion intervals, stationarity was observed, allowing the calculation of Shannon entropy during each part of the signal. The Tables 1 and 2 display the entropy values (in bits) for all rodents

used in the case study during basal and infusion intervals respectively. To find the optimal number of bins for Delayed Mutual Information different numbers of bins were tested on the LFP signals and it provided the number of 256.

The Kolmogorov-Smirnov test performed with rodents groups indicated that there is no difference between the groups at the level of p value equals 10%. Next, Surrogate method was applied. Figure 3 depicts an example of the power spectrum of original signal in comparison to the power spectrum of the surrogate data.

DMI was calculated for surrogate data and original signals. An example result of DMI(Cx,Hp) for rodent R048 can be seen in Figure 4. The lag with maximum mutual information can be also observed: $\tau = 0$ for all rodents used in this case study. The Tables 5 and 6 exhibit the signals bandwidths for each rodent during basal and infusion intervals respectively.

Tables 3 and 7 show, respectively, all channel capacities and transmission rates, simulated during basal interval. The similar results during infusion interval can be verified in Tables 4 and 8. Boxplots in Figures 5 and 6 depict the mean and standard deviation of transmission rate between each brain area considering all the five rodents used to develop the case study.

The computational time to perform this case study was approximately 3 hours for each DMI. Three DMI between each pair of brain areas were computed, resulting in a total of 9 hours. Therefore, for each interval, basal and infusion, it was spent 27 hours, reaching 54 hours total.

Table 1: Entropy calculated for all rodents used in the case study during basal interval. DMI is given in bits.

Rodent	Cx Entropy	Hp Entropy	Th Entropy
R048	15.36	15.36	15.36
R052	13.28	13.28	13.28
R064	14.96	14.97	14.97
R065	15.05	15.05	15.05
R072	15.05	15.05	15.05

Table 2: Entropy calculated for all rodents used in the case study during infusion interval. DMI is given in bits.

Rodent	Cx Entropy	Hp Entropy	Th Entropy
R048	17.39	17.39	17.39
R052	17.02	17.02	17.02
R064	16.62	16.62	16.62
R065	17.14	17.14	17.14
R072	17.29	17.29	17.29

Table 3: Channel capacity in bits for each rodent during basal interval.

Rodent	Cx → Hp	Cx → Th	Hp → Th
R048	1.28	1.42	1.75
R052	3.00	2.93	3.72
R064	0.61	0.65	1.48
R065	1.53	1.51	1.25
R072	2.45	2.40	2.15

Table 4: Channel capacity in bits for each rodent during infusion interval.

Rodent	Cx → Hp	Cx → Th	Hp → Th
R048	0.91	1.26	1.10
R052	1.42	1.51	2.81
R064	0.70	0.71	1.47
R065	1.29	1.42	1.09
R072	2.61	2.72	2.29

Table 5: Bandwidth (BW) in Hertz for each rodent during basal interval.

Rodent	BW Cx	BW Hp	BW Th
R048	1.30	1.49	1.23
R052	1.73	1.71	1.71
R064	9.00	10.50	8.71
R065	10.00	10.00	10.00
R072	2.77	2.75	2.74

Table 6: Bandwidth (BW) in Hertz for each rodent during infusion interval.

Rodent	BW Cx	BW Hp	BW Th
R048	30.00	20.00	20.00
R052	20.00	13.95	10.43
R064	26.00	33.00	36.00
R065	30.00	27.00	30.00
R072	20.26	15.00	20.48

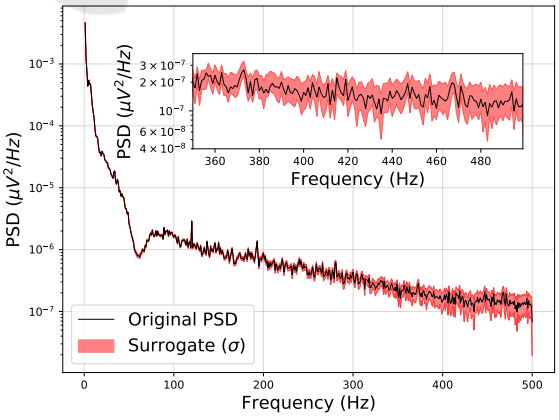

Figure 3: Power spectrum of original cortex signal and surrogate data of cortex area for rodent R048. The power density spectrum of the synthetic data is approximately the same of the original signal.

Table 7: Transmission rate (R) for each rodent during basal interval. Base 2 was used for DMI logarithm. Frequency was measured in Hertz, resulting in *C* being provided in bits and *R* in bits/s.

Rodent	Cx → Hp	Cx → Th	Hp → Th	Hp → Cx	Th → Cx	Th → Hp
R048	3.33	3.69	5.22	3.81	3.49	4.31
R052	10.38	10.14	12.72	10.26	10.02	12.72
R064	10.98	11.71	31.08	12.81	11.32	25.78
R065	38.70	30.2	25.00	30.6	30.2	25.00
R072	6.79	6.65	5.91	6.74	6.58	5.89

Table 8: Transmission rate (R) for each rodent during infusion interval. Base 2 was used for DMI logarithm. Frequency was measured in Hertz, resulting in *C* being provided in bits and *R* in bits/s.

Rodent	Cx → Hp	Cx → Th	Hp → Th	Hp → Cx	Th → Cx	Th → Hp
R048	54.60	75.60	44.40	36.40	50.40	44.40
R052	56.80	60.40	78.40	39.62	31.50	58.62
R064	36.40	36.90	97.68	46.20	51.12	105.80
R065	38.70	30.20	29.43	34.83	42.60	32.70
R072	52.88	55.10	34.35	39.15	55.70	46.90

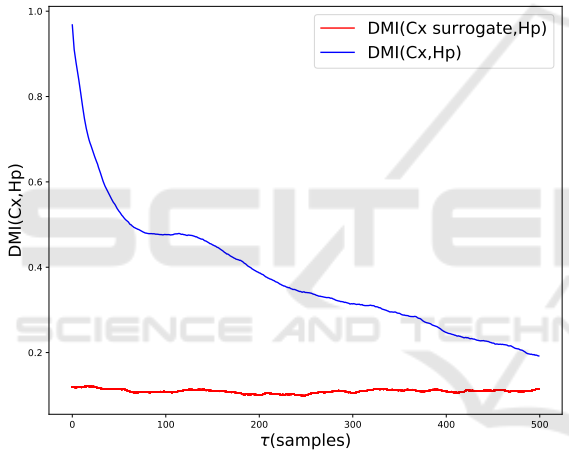

Figure 4: Delayed mutual information between cortex and hippocampus for rodent R048 using 256 bins. The blue line is the DMI performed with original signals and the red lines are the DMI with surrogate. Due to the difference between the surrogate DMI it is not possible to distinguish the difference among surrogate data DMI because it was approximately the same. It is important to note that the lag for maximum mutual information is zero, the same found for another rodents used to perform the case study.

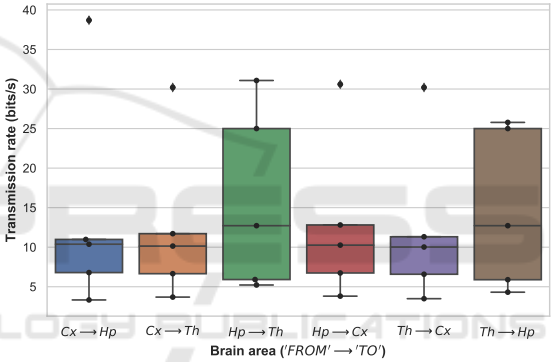

Figure 5: Boxplot denoting the transmission rate in bits/s between each brain areas, for all the 5 rodents used to perform the case study, during basal interval (black dots represent the rodents measures). It is important to observe that the highest standard deviation is verified in transmission rate between hippocampus and thalamus. The black dots represent the rodents in the boxplot.

5 DISCUSSION

The entropy for all rodents used in this case study during basal interval were similar with exception of rodent R052 which was slightly lower. During infusion interval, the entropy was more uniform and higher then calculated for basal interval. This indicates that LFP signals become more probabilistic during infusion, meeting the hypothesis of increase of information rate, which in turn is compliant with the perspective of understanding epileptic seizure as a hyper-synchronisation phenomena.

It is possible to check that signal bandwidth during infusion interval is bigger then the bandwidth during basal interval. This indicates initially larger information for each brain area during infusion, again indicating the increasing communication among cortex, hippocampus and thalamus.

The lag with maximum MI was zero, found for all rodents in this case study. Probably, this result is related with the low sampling rate of LFP signals. All surrogate data created for this case study maintained the power spectrum and randomized the Fourier phases, as expected for IAAFT algorithm, as

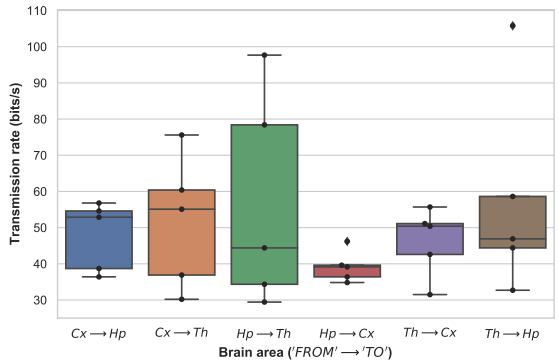

Figure 6: Boxplot denoting the transmission rate in bits/s between each brain areas, for all the 5 rodents used to perform case study, during infusion interval (black dots represent the rodents measures). The values during infusion interval are higher when compared with values measured during basal interval. A possible reason for that difference is a larger signal's bandwidth. The DMI is approximately the same among brain areas for both intervals, see Tables 3 and 4. The black dot represent the rodents in boxplot.

illustrated in Figure 3. This created uncorrelated signals, with whose measures, it was possible to validate the DMI measures for original signals. For all rodents, it was possible to observe that the measures of the original signals were higher than surrogate data measures.

DMI revealed different measures for each rodent even Kolmogorov-Smirnov test indicated statistical equality among groups for 10% significance. Yet, during basal and interval the values for each rodent was approximately the same, indicating that the channel capacity did not change during basal and infusion intervals. Nonetheless, the bandwidth was different between them, resulting in different transmission rates as can be observed in Tables 7 and 8.

It is important to make clear that surrogate analysis assured 5% p-value using Kolmogorov-Smirnov test indicating that signifcance level of comparison between original signals DMI and surrogates DMI for each rodent. When the results are compared between rodents the results presented 10% p-value signifcance level when Kolmogorov-Smirnov test was applied. That is the reason for different Kolmogorov-Smirnov p-values presented in this paper.

The increase of transmission rate, observed for all rodents during infusion interval — in Figures 5, 6 and Tables 7, 8 — is an important result, meeting the concept of hyper-synchronization phenomena that appears during epileptic seizures. DMI was able to capture the increase of communication among brain areas. Since there is more volume of information moving between brain areas during infusion, the uncertainty (entropy) accordingly grows, as expected. The channel capacity practically do not change between intervals, pointing that the main reason for hyper-synchronization is the growth of information sharing between cortex, hippocampus and thalamus.

Delayed Mutual Information represented an another appropriate alternative to existing methods because it was able to provide insights about the functional connectivity among brain areas. It is a non linear method supporting the real world condition that is not linear, do not require a large volume of data when compared to another methods such as Transfer Entropy and it is non parametric which means more flexibility to data analysis.

6 CONCLUSIONS

The use of DMI to perform a case study with rodents LFP presented insights about the communication among brain areas before the occurrence of an epileptic seizure. It was observed that entropy during infusion interval was higher than during basal interval, being the first indicator that the communication was increasing during infusion. The uncertainty about signals was becoming higher. The second indicator was the growth of LFP bandwidth for all signals. It was also observed a consistent lag of zero for DMI for all rodents. This last result may have being influenced by the relatively low sampling rate used to record the LFP signals. The verified channel capacity was different for each rodent, however, exhibited the same behaviour of staying approximately equal during basal and infusion intervals. Consequently, the transmission rate was different between periods mainly due to the change of signal's bandwidth. It indicates that communication is increasing essentially due to the growth of information sharing among brain areas. This is the last indicator, which is in agreement with the idea of hyper-synchronisation phenomena associated with epileptic seizure. Therefore, DMI represented a helpful method to perform functional analysis on LFP signals.

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