EEG SIGNALS IN EPILEPSY AND MIGRAINE
Analysis and Simulations by Multi-agent Systems

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Abstract: The preliminary results of some observations carried out on the spectral content of EEG signals from migranious and epileptic individuals and, in particular, on the spatio-temporal correlation of the neuronal activation in the two pathologies, are presented. In the aim to simulate the qualitative features of EEG signals associated to migraine and epilepsy, we used a computational approach based upon Pearson correlations and a Multi Agent System. Our findings, although still not conclusive, revealed considerable heuristic power on the sole assumption of a similar synchronization process of the underlying neuronal population, and may provide in the long term useful hints to a very difficult problem.

1 INTRODUCTION

According to the World Health Organization, epilepsy is one of the most common neurological disorder and its prevalence in the total world population is of the order of about 1%, with no major geographical bias. Migraine, on the other hand, although less severe as a disorder, is much more common and its well known worldwide distribution, according to some hypothesis, linked to economic levels and life styles (Lipton and Bigal, 2005).

It has been suggested some time ago (Sack, 1992; Ottman and Lipton, 1996) that epilepsy and migraine are correlated, indicating that a crucial role in both pathologies is played by an abnormal synchronization of the involved neuronal populations. This has been recently reassessed (Rogawski, 2008) on the basis of accurate epidemiological data (Fig. 1). Thus, recruiting a larger and larger number of phase-coupled neurons, should account for: i) the peculiar activity bursts appearing in EEG signals; ii) the close temporal correlation of the activity bursts with macroscopic clinical symptoms like epileptic seizures or individual perceptions like visual aura; iii) the typical rythmic occurrence and spatial patterns of the activity waves. Such apparently simple phenomena appear amenable to simulation, taking advantage of the continuous increase in hardware power and flexibility/sophistication of simulation environments (Brette et al., 2007).

We report here the preliminary results of a study on the common features of EEG signals associated to migraine and epilepsy which include: i) a systematic correlation of the spectral content of the EEG signals recorded from individuals with diagnosis of focal and diffused epilepsy and of migraine, and ii) a simulation study of the shift from random to synchronous activity within an artificial Multi Agent System.

2 METHODS

2.1 EEG Records and Exclusion Criteria

The EEG signals analyzed in this work have been recorded in the Dept. of Neurological Sciences of Univ of Rome - Sapienza, according to the standard protocol (Flink et al., 2002) and using a 10–20 montage, except in the case of the migraine signals, which came from the Australian EEG Database (Hunter et al., 2005). The exclusion criteria used by clinicians to select the signals included the absence of

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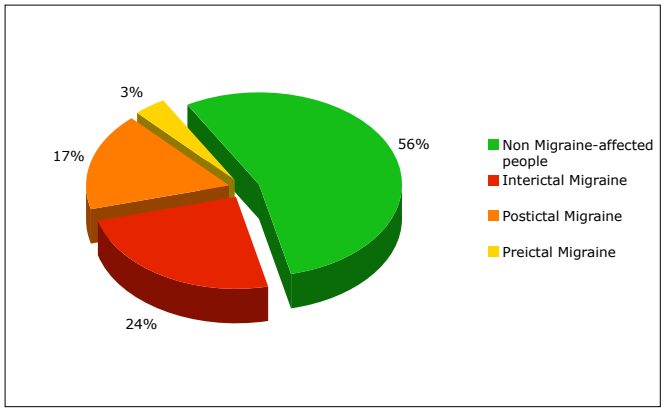

Figure 1: Statistics about the migraine and epilepsy comorbidity. The illustration shows the prevalence of migraine disease in a Norwegian epilepsy-affected population. (Data from table 2 in (Syvertsen et al., 2007).)

any pharmacological, psychiatric or behavioral interference potentially able to produce signal alterations.

2.2 Data Analysis

The software toolset used in this work included a number of macros written in the programming language of MatLab (Mathworks, 2006), JMP (SAS, 2007) and NetLogo (Wilensky, 2009), and are freely available upon request. The data analysis procedure can be summarized in the following steps:

- The digitized EEG signals produced by the classical 10 - 20 montage of the electrodes, described in (Flink et al., 2002), were carefully cleared from artifacts, as identified by the clinical experts. Whenever the artifacts were only present in some of the signals, all records from that montage were submitted to the identical clearing procedure, in order to preserve their phasing.
- The digitized signal (recorded at a 256 Hz) from each electrode was 'windowed' in stretches of about 8 sec. For example, from a 5-minutes-lasting record, 62 windows were obtained, which typically reduced to about 40 after the above described artifact clearing.
- The spectral content of the signal in each window was obtained by a macro based upon the DFT procedure of MatLab (Mathworks, 2006), and the power spectra of the windows derived from each electrodic record were aligned in a matrix of typical size = 20 (windows) * 50 (frequencies in Hz).
- The above matrices (corresponding to whole electrodic records) were correlated by means of the Pearson correlation coefficient (R) :

$$R = \frac{\sum_{i=1}^{n}(Y_i - \bar{Y})(X_i - \bar{X})}{\sqrt{\sum_{i=1}^{n}(Y_i - \bar{Y})^2}\sqrt{\sum_{i=1}^{n}(X_i - \bar{X})^2}} \qquad (1)$$

Positive and negative values indicate that the two variables show the same or, respectively, an opposite trend with respect to each other. Close to zero values indicate the absence of any significant linkage. For a complete survey of the Pearson Correlation Coefficient as a powerful data analysis tool, see (Rodgers and Nicewander, 1988).

2.3 Multi Agent System (MAS)

Multi agent systems (MAS) are useful for simulating the highly cooperative behaviour of individuals in social groups like human communities, insect colonies nests or multicellular organisms (Russell and Norvig, 2005). In a neuroscience context, the architecture of the agent system is such that each agent corresponds to a neuron or a neuron class and is able to send signals according to its neighbours, thus influencing their activation state. The activation time of the single agent may also change according to afferences of connected fibers, regulating the activation threshold as well as the firing frequency. A MAS system should be able to reproduce the EEG signal typical of migraine or epilepsy. The more or less realistic conditions under which this may be achieved, could be taken as reinforcing/disproving the theory that the basis of both pathologies is a common synchronization mechanism.

3 RESULTS

3.1 Correlating Signals from Homo - and Controlateral Electrodes

An interesting trend is shown by correlating traces from symmetric couples of electrodes in the two

hemispheres within the same subject. Table I contains the Pearson coefficients obtained by coupling: i) corresponding electrodes in the two hemispheres, ordered in the rostro-caudal direction, from the fronto-parietal electrodes (F_{p1},F_{p2}) to the occipital (O_1,O_2) lobes (columns 1,2,3), and ii) electrodes of the same (left) hemisphere (columns 4,5).

Table 1: Time dependent Pearson correlations between left and right emisphere in different pathologies (S1, S2 = Migraine; S3 = diffused epilepsy; S4 = focal epilepsy; S5 = control). The correlations were calculated from the records of the following couples of electrodes: Fp = frontal-pole; T = temporal; O = occipital. Odd and even suffixes refer to right and left emispheres, respectively; values higher than 0.66 are in bold.

		Fp_2	T_4	O_2	T_3	O_1
$S1$	Fp_1	**0.77**			0.35	0.34
	T_3		**0.67**			0.52
	O_1			**0.77**		
$S2$	Fp_1	**0.79**			0.26	0.15
	T_3		0.49			0.22
	O_1			**0.82**		
$S3$	Fp_1	0.30			-0.04	0.28
	T_3		0.23			0.08
	O_1			0.50		
$S4$	Fp_1	0.58			0.15	0.40
	T_3		0.22			0.08
	O_1			0.63		
$S5$	Fp_1	0.53			0.22	0.34
	T_3		0.16			0.14
	O_1			0.64		

In all cases, the correlations were carried out over subsequent, non overlapping windows of 2000 points each, from signals of about 64,000 points sampled at 256 Hz. The aim was to check whether in the time spanned by the signal, namely within the about 138 sec of its total duration, some significant spectral change occurred. An even more ambitious goal was to enlight a space-dependent trend linked to the rostro–caudal direction.

Although the data in Table I did not substantiate clearly the above expectations, it seems fair drawing, on their basis, the following minimal conclusions: a) all the analyzed signals show a quite synchronous behaviour, between the left and right emispheres, in the fronto-parietal and occipital lobes; b) the signal associated to the migraine diagnosis shows the highest correlation as compared to both the epileptic cases; c) the highest synchronous activity is concentrated in the occipital lobe under all conditions. Moreover, the concomitant lower and higher synchronization in the temporal/central and frontoparietal areas, respectively, are consistent with an oscillating behaviour, namely a clustering in well defined areas of the maximal and minimal activity occurring in the considered time span. It is worth mentioning that a similar (although less clear) trend is also observed by correlating EEG records from proximal electrodes within the same (left) hemisphere, reported in columns 4,5 of Table I. The data concerning the other (right) hemisphere are almost the same.

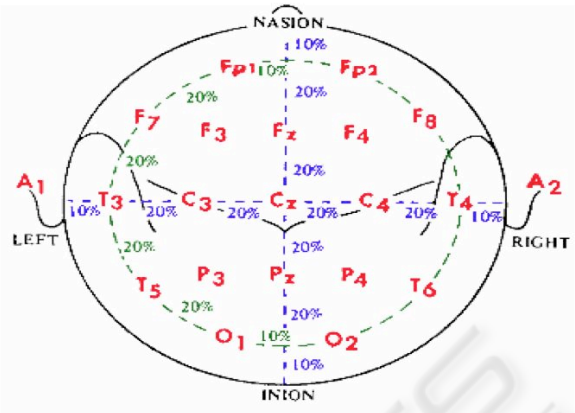

Figure 2: Electrode location on the human scalp in the "10-20 montage". According to a standardized procedure 10 small electrodes (less than 1 cm diameter, wetted by a salt-past increasing the electrical conductivity) are symmetrically located on each emisphere according to the following nomenclature: Fp = frontal-pole; T = temporal, C = central, P = parietal, O = occipital.

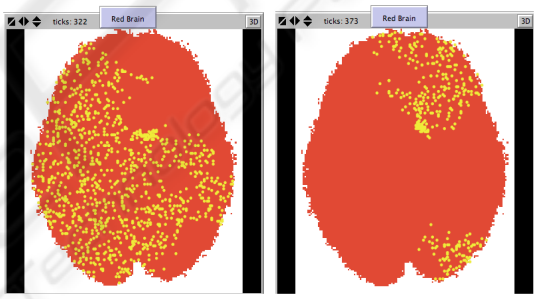

Figure 3: Oscillating activity of brain neurons simulated by a MAS (Wilensky, 2009). Left and right panels refer to the main peaks of activity within a single oscillation cycle. Each cycle lasted about 10 machine time units, corresponding to about 1 s, and involved 1500 agents in both hemispheres, whose behaviour was initially random. The oscillating regime apparent in the two panels arises after about 350 machine time units. The algorithm used in the simulation has been described in detail elsewhere (Colosimo, 2008)

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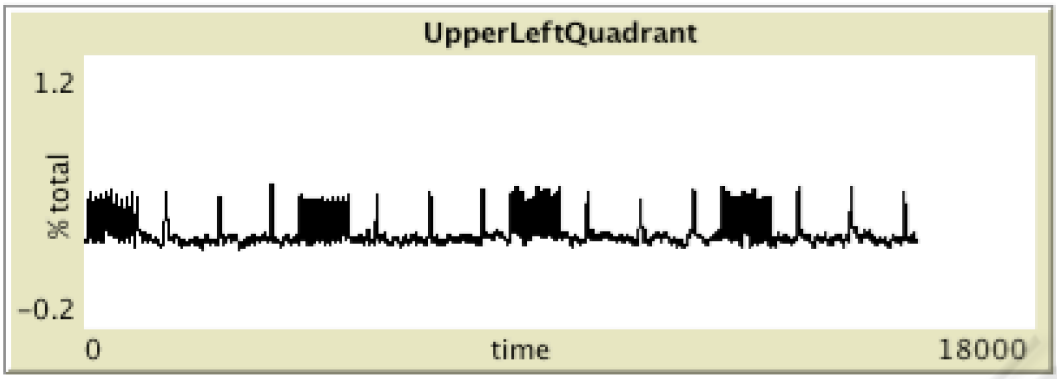

Figure 4: A MAS based oscillating field model for simulating hypersynchronized neuron waves. In this case the two brain hemispheres have been divided into four identical quadrants and the fraction of the total (5,000) neurons active in one the quadrants reported.

3.2 Simulating Cortical Spreading Depression

The first conjecture about the causal relationships linking synchronization and epilepsy dates back to Matsumoto (1964),(Matsumoto and Ajmone-Marsan, 1964) showing that hyperactivity of a limited number of cells unable to recruit a larger network was also unable to originate an epileptic event. The somehow paradoxical discovery of the extensive synchronization occurring in migraine is due to Leao (Leao, 1944), while studying an epileptic model in rabbits. Leao observed a depolarizing wave moving at a 3 mm/min speed in the rabbits cortex. He named the wave Cortical Spreading Depression (CSD), since after its passage the cortex remained inactive for some time. Only in 1994, however, Lauritzen (Lauritzen, 1994) hypothesized that CSD could have been at the origin of the visual aura in human migraine. He showed that associated with the visual aura was a high-activity wave moving in the anterior direction from the occipital region at speed from 2 to 6 mm/min. Such a wave was followed by a temporary suppression of the cortical electrical activity. The frequent absence of the visual aura in many subjects has been explained by assuming that CSD may also originate in visually silent regions (Pietrobon, 2005). CSD, in fact is not limited to the occipital area: its starting point may be observed most frequently in the CA1 hyppocampal area, followed by the neo-cortex, and it remains a most interesting phenomenon of neural synchronization.

Figure 3 shows the activity patterns observed in the area representing a coronal section of the human brain, by means of a simulation device described elsewhere (Wilensky, 2009). The 2 panels in the figure show the clustering of active neurons in different regions of the ”brain” during a repeating functional cycle. The period of such cycle can be easily modulated by a number of factors, primarily of metabolic nature.

4 CONCLUSIONS

Even if neither migraine nor epilepsy are actually fully understood in their deep causes and detailed mechanisms, a most probable connection between them concerns the abilitiy of neural cells to get pathologically hypersynchronized under various circumstances. In this frame, it is maybe worth stressing that the main goal of our research plan, is to simulate the cortical depression wave dynamics. Although obviously related to the synchronized activity of neuron populations, this represents a higher level of complexity, since it involves both a time and space dependence of the oscillatory activity whose reproduction in silico, at our knowledge, has not been successfully attempetd as yet.

All in all, the most interesting outcome of our study may be summarized as follows:

- Concerning the analysis of EEG signals, a necessary prerequisite to any modelistic effort, a simple and flexible tool like the Pearson correlation coefficient showed considerable heuristic power: as a matter of fact Figures 3,4 and Table I indicate that by just dissecting the time series into a number of subsequent windows in order to increase the resolution of the method, allowed to identify the presence of time and space ordered activity patterns of neurons from both homo- and contralateral signals.

- Concerning the multi-agent simulation environment, NetLogo (Wilensky, 2009)appeared more flexible as compared to other programmable tools specialized for neuronal systems, like, for example, Gene-

sis (Beeman and Bower, 2009) or Neuron (Carnevale and Hines, 2006), although probably less powerful in terms of manageable models sizes. (Brette et al., 2007) As an example, by the very same tool (Netlogo) it was relatively straightforward to work out simulations as those shown in figures 3 and 4.

- Although still far from conclusive, our results and, in particular, the similarity of the simulated signals in figure 4 with the alternating bursts of activities and 'interictal' phases, observed *in vitro* (Panuccio et al., 2009) and *in vivo* (Steriade, 2006), represents an encouraging first step towards the clarification of neural pathologies by means of relatively simple and flexible numerical methods.

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