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# Global Interactions Analysis of Epileptic ECoG Data

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**Abstract.** Localization of the epileptogenic zone is an important issue in epileptology, even though there is not a unique definition of the epileptic focus. The objective of the present study is to test ultrametric analysis to uncover cortical interactions in human epileptic data. Correlation analysis has been carried out over intraoperative Electro-Corticography (ECoG) data in 2 patients suffering from temporal lobe epilepsy (TLE). Recordings were obtained using a grid of 20 electrodes (5x4) covering the lateral temporal lobe and a strip of either 4 or 8 electrodes at the mesial temporal lobe. Ultrametric analysis was performed in the averaged final correlation matrices. By using the matrix of linear correlation coefficients and the appropriate metric distance between pairs of electrodes time series, we were able to construct Minimum Spanning Trees (MST). The topological connectivity displayed by these trees gives useful and valuable information regarding physiological and pathological information in the temporal lobe of epileptic patients.

**Keywords:** Multivariate, ultrametricity, time series analysis

**PACS:** 05.45.Tp, 05.45.-a, 02.50.Sk

## INTRODUCTION

Drug-resistant temporal lobe epilepsy (TLE) can be treated by tailored surgery guided by electrocorticography (ECoG). Based on this and other pre-surgical data, the anterior lateral temporal cortex, portions of the amygdala and the hippocampus are commonly excised [1]. The goal of surgery is to achieve seizure control. However, while some patients are seizure free or show a significant reduction of seizure activity after surgery, others show no changes or even worsen [2]. It is therefore important to improve our understanding of the lateral and mesial dynamics in the temporal lobe of epileptic patients.

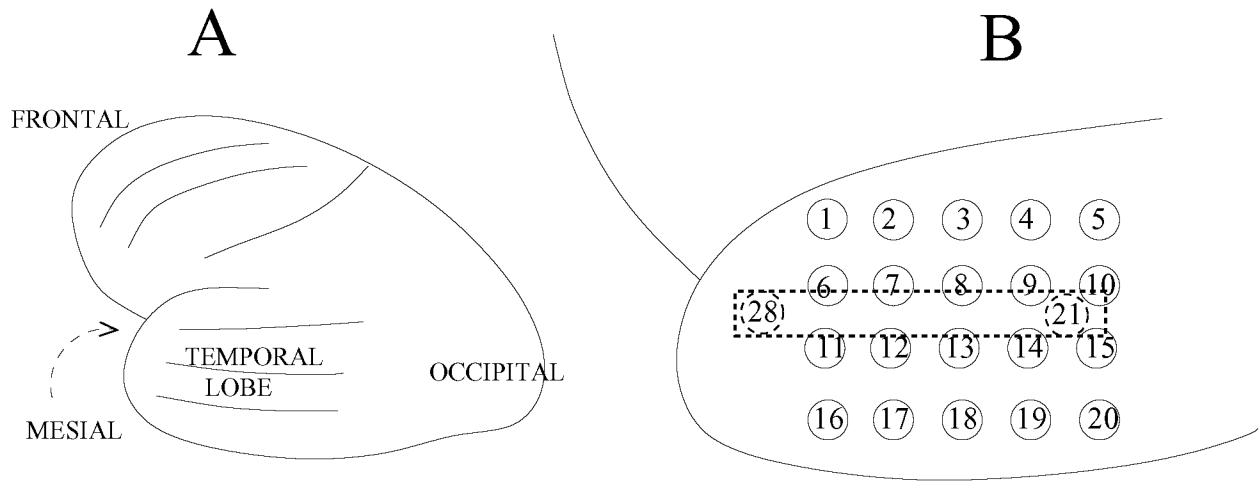
Even though several regions has been identified as involved in the epileptic pathology [3], no single area is solely responsible of the clinical seizures. On the contrary, an interplay among different areas seems to play a central role in triggering the seizure onset. Moreover, the relation between interictal (in between crisis) and ictal (during the crisis) areas are still debated [4]. It is therefore important to develop novel approaches to uncover underlying cortical dynamics in the epileptic patients. A better understanding of the functional connectivity in the epileptic cortex would provides new insights in the clinical and surgical treatment of the epileptic patient.

In the present work, we apply a multivariate graphical method, such as the Minimum Spanning Tree (MST) construction, in order to characterize global interactions in the temporal lobe of epileptic patients. As we shall show, MST seems to correctly display lateral-lateral and lateral-mesial interactions. Because the intrinsic relation between the MST construction and ultrametric spaces [5], we shall introduce in the methodology section the link among both topics. It seems that the connection topology resulting from our present work could it be relevant from the point of view of the surgical procedures carried out in the patients.

## DATA AND METHODOLOGY

### Data sets

We shall apply MST methodology to two drug-resistant TLE patients, who underwent surgery at the Epilepsy Unit of the Hospital La Princesa. Informed consent and approval by the local ethic committee were obtained. Patients were evaluated intraoperatively with 4x5 subdural electrode grids and a strip of either 4 or 8 electrodes, with an interelectrode distance of 1cm. The strip is inserted in the inner part of the temporal lobe, also known as the mesial area. In panel A of Figure 1 a rough sketch of the whole brain is depicted, showing the approximate location of the



**FIGURE 1.** A: Sketch of the brain (lateral view), with the frontal, occipital and temporal lobes depicted. B: Zoom of the temporal lobe with the electrode grid (5x4) over the lateral temporal cortex and the electrode strip (dotted line) inserted into the inner i.e. mesial, area of the temporal lobe. Only the first and last strip electrodes are shown for the sake of clarity

temporal lobe. In panel B, position of the electrodes grid in the lateral (outer) side of the temporal lobe, and the electrode grid in the mesial (inner) side of the temporal lobe is also shown.

Intraoperative ECoG was recorded during 15-20 min using a 32-channel amplifier (Easy EEG II, Cadwell, USA). Epochs lasting from 3 to 5 minutes were selected free of artefacts by visual inspection. By using consecutive, non-overlapping windows of 1024 data points (5.12 seconds at 200 Hz sampling rate) we obtain records of 16384 data points in each of the 24 or 28 channels. This time window selection allows encompassing most of the nonstationarities included in the time series. All analysis programs were written in Fortran and the R package has been used in the circular MST plot generation.

## Methodology

There exist an intrinsic relation between clustering methods such as the MST and ultrametricity [5]. In fact, distance on a MST between two sites are actually ultrametric distances. Thus we shall introduce in this section some mathematical definitions and constructions used lately in the paper, relating ultrametric distances and MST.

In order to quantify the degree of similarity between pairs of electrodes' time series, we have calculated the Pearson correlation coefficient [6] between electrodes  $e_i$  and  $e_j$

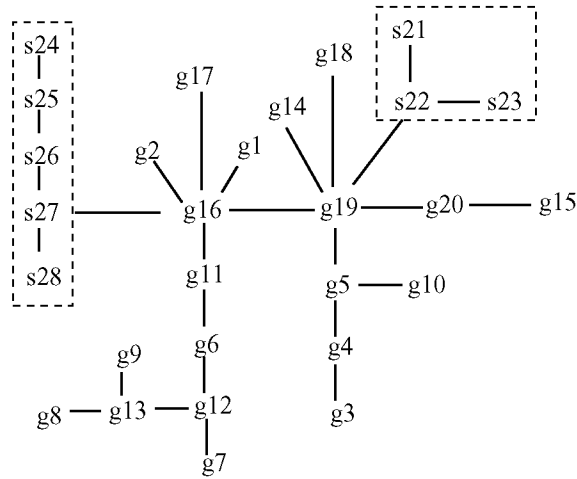
$$\rho_{i,j} = \frac{\sum_{k=1}^N (e_i(k) - \langle e_i \rangle)(e_j(k) - \langle e_j \rangle)}{\sqrt{\sum_{k=1}^N (e_i(k) - \langle e_i \rangle)^2} \sqrt{\sum_{k=1}^N (e_j(k) - \langle e_j \rangle)^2}} \quad (1)$$

where  $\langle e_i \rangle$  is the mean value of channel  $e_i$  in the period considered. Because  $\rho_{i,j}$  is a measure of similarity, and a measure of "distance" is actually needed in order to construct an ultrametric space [5], following Gower [7], we define the distance between the time evolution of channels  $e_i$  and  $e_j$  as,

$$d(i,j) = \sqrt{\rho_{i,i} + \rho_{j,j} - 2\rho_{i,j}} = \sqrt{2(1 - \rho_{i,j})} \quad (2)$$

The last equality came from the simetry property of the correlation matrix,  $\rho_{i,j} = \rho_{j,i}$  and the normalization  $\rho_{i,i} = 1 \forall i$ . In this way,  $d_{i,j}$  fullfils the three axioms of a distance:

- $d(i,j) = 0$  if and only if  $i = j$
- $d(i,j) = d(j,i)$
- $d(i,j) \leq d(i,l) + d(l,j)$



**FIGURE 2.** MST of patient # 1. Letter g stands for grid and letter s stands for strip

The third axiom, the triangular inequality, characterizes a metric space. An *ultrametric space*, on the other hand, is endowed with a distance that obeys a stronger inequality, the *ultrametric distance*  $d(i, j)^<$ :

$$d(i, j)^< \leq \text{Max}\{d(i, l), d(l, j)\} \quad (3)$$

Thus, it follows that the distance matrix given by Equation (2) satisfies ultrametricity.

One method to obtain  $d(i, j)^<$  directly from the distance matrix  $d(i, j)$  is through the MST method [5]. Given the metric space  $(\Omega, d)$ , in our case, channels time series as the elements of  $\Omega$  and the distance defined by Equation (2), there is associated with this space a nondirected graph with the same elements of  $\Omega$  as vertices, and edges between the adjacent elements  $(i, j)$ , the distance  $d(i, j)$ . The MST is a tree with the same vertices as in  $\Omega$  but of minimal total length. When there is a MST on  $\Omega$ , the distance  $d(i, j)^<$  between two elements of  $i$  and  $j$  in  $\Omega$  is given by,

$$d(i, j)^< = \text{Max}\{d(w_i, w_{i+1}), 1 \leq i \leq n - 1\} \quad (4)$$

where  $C_{i,j} = \{(w_1, w_2), (w_2, w_3), \dots, (w_{n-1}, w_n)\}$  denotes the unique path in the MST between  $i$  and  $j$  ( $w_1 = i, w_n = j$ ).

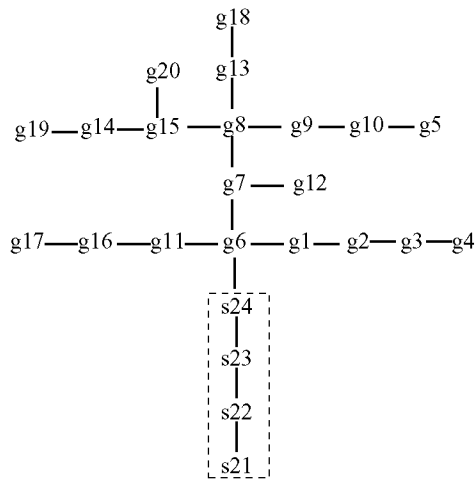
In this way, given a topological tree such as the MST, by using as elements of  $\Omega$  the ECoG channels' time series, distances between any two such time series turns out to be ultrametric. It remains however to know if the topology spanned by the used time series it is in fact ultrametric. As shown by Murtagh [9], epileptic EEG time series can be very well embedded in an ultrametric topology. Thus, we shall apply confidently the MST construction for the ECoG time series in order to explore the topological relations between the cortical sites in epileptic patients.

## RESULTS

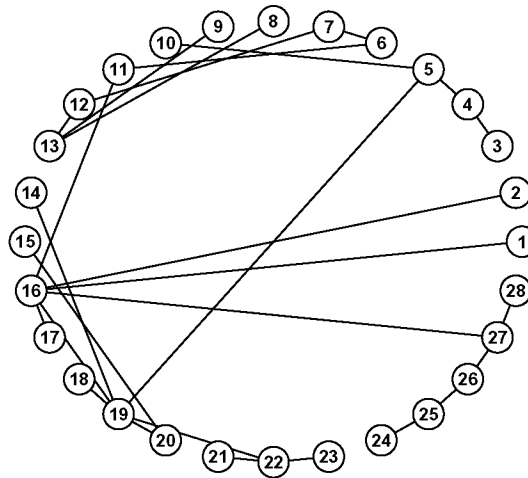
### Global Interactions

As an example of the present methodology, we have used ECoG data from two patients. In one case (patient # 1) a grid of 20 electrodes is located in the lateral area and a strip of 8 electrodes is located in the mesial area, both in the temporal lobe. In the other case (patient # 2), the mesial strip of 8 electrodes is replaced by a 4 electrodes strip. We shall analyze therefore a multivariate register of 28 simultaneous time series in patient # 1 and 24 simultaneous time series in the patient # 2. From now on, we shall identify cortex location with the electrode position at that site. For instance, in talking about the position 17 (or g17) we are actually referring to the position covered by the electrode 17.

Correlation matrices has been calculated through equation (1) for each pair of electrodes  $e_i$  and  $e_j$ , in temporal windows of 1024 data points each (5.2 seconds). A final correlation matrix is obtained by averaging 16 consecutive, non-overlapping windows. Distance matrices in both patients were obtained through Equation 2 and the Minimum Spanning Trees is obtained in each case by using the Kruskal algorithm [8]. Figure 2 shows the MST for patient # 1 and Figure 3 shows the MST for patient # 2.



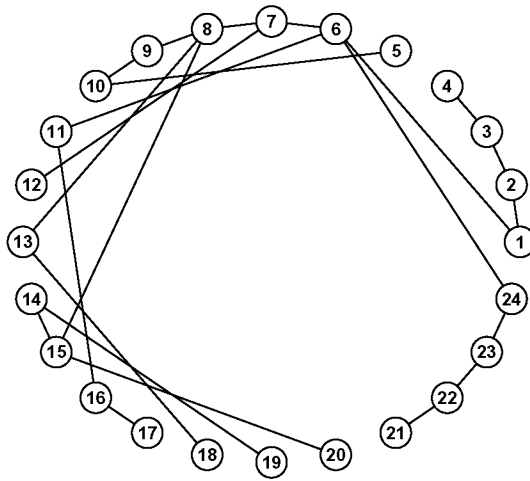
**FIGURE 3.** MST of patient # 2. Letter g stands for grid and letter s stands for strip



**FIGURE 4.** Circular MST of patient # 1

MST for patient # 1 shows (Figure 2) the interaction connectivity. Channels g1 to g20 corresponds to the grid and s1 to s8 to the mesial strip. Particular locations seems to play central roles in the interactions dynamics, mainly because the higher number of its connections, as for example sites g16, g19 and g12. Location around g12 is a "local" cluster of interactions. However, locations around g16 and g19 involves more than local interactions. In the case of g16, there exist a clear link between this site in the lateral cortex and those of the inner part of the lobe, in the mesial area, through the location s27. Moreover, this lateral site not only is linked with its first neighbors, g11 and g17, but also with relative distant sites in the lateral cortex, as are sites g1 and g2. The same situation seem to happened with site g19, which it is linked to the mesial strip through the site s22 and with relative distant lateral sites as g5.

The other case, patient # 2 it is depicted in Figure 3. In this case, the mesial strip is composed of only four electrodes.



**FIGURE 5.** Circular MST of patient # 2

The two positions with maxima number of connections are g6 and g8. g6 it is directly linked to the inner part of the temporal lobe. Its other connections, namely, g1, g7 and g11 are purely local. In the case of g8, also, all of its connections are almost local, except in the case with g15 position, which however, it is relatively close. In the overall analysis of this case, it seems that there exist only local interactions, both in the lateral and in the mesial part of the temporal lobe.

In order to see in a more clear way the kind of interactions in both cases, one can replot regularly the electrodes numbers on a circle, as we have done in Figure 4 (patient # 1) and Figure 5 (patient # 2). In this format, it is expected that local (first neighbor) interactions in position  $i$  range at most to position  $i \pm 5 \pm 1$ , with the exception of the lateral-mesial interactions. In Figure 4 for patient # 1, even though most of interactions are local, there exist however three links which involves long range connections. These are g1-g16, g2-g16 and g5-g19. The other apparent long range interaction is the lateral-mesial connection through the g16-s27 link.

In the other case, however, all of its interactions are local, with the exception of the g8-g15, which however it is not of the long-range type.

## Surgical outcomes

The next step was to compare the electrodes topological information obtained through the MST construction against the surgical procedure, that is, the removed areas in the surgery. During the surgery, the neurosurgeon proceed to remove part of the lateral temporal cortex, accordingly with the neurophysiologist indications.

In the case of patient 1, the following lateral cortex sites: 6, 7, 8, 11, 12, 13, 16, 17 and 18 has been removed. Note that even though one of the two most connected areas, i.e. site 16, has been removed, the other one, namely, area 19 has not been removed. As we have noted previously, area 19 seems to be a critical one regarding functional connectivity in the lateral cortex, because the following two facts. In the first place, it link long distance areas, like site 5 with site 19, and in this sense, it seem to play the role of a "small world" link [10] between distant cortical areas. In the second place, it also serves as a link between lateral and mesial areas, because site 19 it is directly connected between distant cortical areas. On the second place, it also serves as a link between lateral and mesial areas, because site 19 it

is directly connected to the mesial area through site 22. In this case, though the number and intensity of the epileptic crisis has been reduced, the patient remains from suffering epileptic crisis after the surgery.

In the second patient, during the surgery, the neurosurgeon has removed lateral sites: 7, 8, 11, 12, 13, 16,17,18 and 19. Even though in this case there no exist long range interactions as in the first patient, however, one of the two most connected sites, that is, site 6, has not been removed. Moreover, this site is the direct link between the lateral area and the mesial one. Also in this case, the number and intensity of epileptic crisis has been substantially reduced, the patient still suffer casual crisis.

## CONCLUSIONS

In the present work we have used ultrametric analysis in order to uncover global cortical interactions in the temporal lobe of epileptic patients. By using the distance matrix between ECoG's channels's time series, we were able to construct an ultrametric space. Linked with the ultrametric space, we have constructed a MST which display the functional connectivity in the temporal lobe. Both intra-lateral and lateral-mesial interaction seems to be correctly displayed. The methodology exposed is applied in two cases of TLE patients. In one case, patient # 1, not only local interactions are present, but on the contrary, long range interactions are apparent in the lateral side of the temporal lobe, as a kind of "small world" effect. In the other analyzed case, only local interactions are present in the lateral area.

By looking at the removed cortical areas during the surgery, our results indicate that if the most connected sites are not removed, some kind of epileptic crisis will remain. However, it must beared in mind that our results are only indicatives and it would serves as a line of investigation in this direction, which is now carried out by our group.

## ACKNOWLEDGMENTS

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