On Spatio-Temporal Dependency Changes in Epileptic Intracranial EEG: A Statistical Assessment

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Abstract—**Pathological manifestations of epilepsy are generally associated with a set of clinical events that possess both spatial and temporal patterns. In this paper, based on a similar hypothesis, we study the evolution of epileptic seizures by analyzing temporal changes in the spatial bindings between various cortical structures. We propose to apply the Mantel statistics to quantitatively analyze the temporal changes in spatial-correlation matrices. The Mantel test is applied to 6 complex partial seizures of an epileptic patient. We show that, in 5 of the 6 instances, the spatial structures undergo significant connectivity changes in the 2 hours time-interval prior to the occurrence of a seizure.**

I. INTRODUCTION

It is widely suggested that certain clinical manifestations of epilepsy are directly reflected in the changes associated with temporal dynamics of the brain. Much of the previous studies [1-8] have focused on analyzing the temporal changes associated with brain's non-linear dynamics. Feature descriptors such as system's complexity or the short-term Lyapunov exponents [2-6] are analyzed and studied individually on each of the system's dimensions. Temporal dynamical changes associated with such features, however, fail to explain state associated changes of an epileptic brain in its overall spatial configuration. Rather than studying the temporal dynamics along each dimension individually, the emphasis should be on considering all the dimensions in unison in a multi-variate perspective. In other words, in spatially extended systems, dynamics change both in time and in space and therefore, approaches that track the temporal changes of the spatial networks can be more effective and helpful in efforts aimed at characterizing clinical events, such as epileptic seizures.

Inspired by the similarity–index technique (SI) introduced by Arnhold *et al.* [9], we have recently proposed a SOM based computationally efficient measure, the SOM-SI [10-12], to quantify mutual interactions among various nodes in a spatially coupled multi-dimensional system. The affinity matrix representation formed from the interdependency measurements provides information on the interactions among all the possible pairs of nodes in a graph. For an epileptic brain, in particular, changes associated with the epileptic activity will therefore be reflected by temporal changes in the overall spatial connectivities. In this study, we discuss a statistical approach to quantitatively track those temporal changes in the overall spatial-patterns of an epileptic intracranial EEG. In particular, we propose to evaluate the similarities in spatial connectivity's using Mantel statistics, a well known statistical approach designed specifically to quantify similarities between affinity matrices. The paper is organized as follows: We first present a brief review of Mantel test procedure in section II. Section III discusses the application of the Mantel statistics to epileptic intracranial EEG and the corresponding results. In section IV we discuss about potential directions for future study.

II. MANTEL TEST FOR MATRIX COMPARISON

The Mantel test was first developed in 1967 to correlate temporal and spatial distributions of cancer incidences [13] and since then it has been widely used as a correlation tool in various biological [14] and ecological disciplines [15-17]. It is a linear correlation estimate of the relationship between two square distance matrices based on the degree of relationship of two sets of variables taken at the same sampling locations. In short, the Mantel test is essentially a statistical framework to test the consensus of two distance/proximity/affinity matrices.

In the Mantel test, the hypothesis is that the distances (or similarities) in matrix A are independent of the distances, for the same set of objects, in another matrix B. In other words, we test the hypothesis that the two matrices under study are no more similar than they would be by chance assignment of the labels to the rows and corresponding columns. The normal procedure to test the hypothesis would be to compute a measure of resemblance between the values in the two upper (or lower) triangular parts of the square symmetric matrices under comparison and test against a random distribution. The random distribution is constructed by repeatedly permuting at random, the rows and corresponding columns of one of the matrices, and re-computing the statistic. Finally, the original value of the statistic is compared with the distribution obtained by randomly reallocating the order of the elements in one of the matrices.

The statistic used for the measure of correlation between the matrices is the classical Pearson correlation coefficient:

$$r = \frac{1}{N-1}\sum_{i=1}^{N}\sum_{j=1}^{N}\left[\frac{A_{ij}-\overline{A}}{s_A}\right]\left[\frac{B_{ij}-\overline{B}}{s_B}\right] \qquad (1)$$

where N is the number of elements in the lower or upper triangular part of the matrix, $\overline{A}$ is the mean for A elements and s_A is the standard deviation of A elements. If the two matrices are normalized, i.e.

$$a_{ij} = \frac{A_{ij}-\overline{A}}{s_A};\ b_{ij} = \frac{B_{ij}-\overline{B}}{s_B},$$

we have $\overline{a}=0,\ s_A=1,\ \overline{b}=0,\ s_B=1,$ and therefore (1) can be re-written as

$$r = \frac{1}{N-1} \sum_{i=1}^{N} \sum_{j=1}^{N} a_{ij} b_{ij} \qquad (2)$$

Note that the coefficient *r* measures the linear correlation; therefore if any non-linear relationships exist, they will be lost. The testing procedure using the Mantel test statistic can be summarized as follows:

Assume two square symmetric matrices A and B of size N x N. The rows and columns in both the matrices correspond to the same objects. The first step is to compute the Pearson correlation coefficient between the corresponding elements of the lower (or upper) triangular matrices.

1. Compute the original (or the non-permuted) statistic r_{AB} using (2)
2. Permute randomly the rows and the corresponding columns of one of the matrices (say B) to create a new matrix B'.
3. Recompute (1) using A and B' to obtain permuted statistic $r_{AB'}$.
4. Repeat the steps (2) and (3) several times (> 500) to form a distribution of the permuted statistics. This distribution will be the reference distribution under the null hypothesis.
5. Assuming normal approximation on the reference distribution, compute the z-score by comparing the non-permuted statistic in step (1) with the mean and variance of the reference distribution. i.e,

$$z = \frac{r - \bar{r}'}{\sigma_{r'}} \qquad (3)$$

III. APPLICATION TO EPILEPTIC INTRACRANIAL EEG

In the current study, we propose to use the Mantel-test statistic to compare SOM-SI affinity matrices, evaluated at different time periods. Particularly, the emphasis will be on tracking the temporal changes of the spatial connections, in the intervals prior to seizure. The experimental design procedure is explained in the following steps.

1. Select 2 hours of intracranial EEG segments prior to a seizure.
2. Quantify pair-wise spatial dependencies among the channels (in this case 24) using the SOM-Similarity Index measure. The SOM-SI affinity matrices are obtained from 10 second windows, for 2 hours pre-seizure (only the alternate 10 seconds are evaluated; therefore we get a total of 180 SOM-SI affinity matrices from 2 hours data). In our study, the 24 channels were sampled from orbito-frontal, temporal depth and the sub-temporal depth regions of an epileptic brain.
3. Fluctuations between successive matrices are smoothened by temporal averaging. A window size of 3 (equal to 1 minute) was used.
4. Affinity matrix corresponding to the window 2 hours prior to seizure is individually compared with the affinity matrices at all other times leading to a seizure. For comparison, every 3rd minute was used to ensure that the effects of correlation between matrices due to temporal averaging were eliminated. Note that the null-hypothesis distribution was formed from 700 randomly permuted statistics.
5. Hypothesis testing is done by checking the z-scores at the 95% significance level.

The Mantel test statistic was applied to six complex partial seizures of a patient, suffering from medial temporal lobe epilepsy. Fig. 1 illustrates the temporal changes in the spatial-activity of the channels, in the interval 2 hours prior to seizure. z_α scores greater than $z_{crit,0.95} = 1.96$ indicates that the null hypothesis H_0 is rejected at the 95% significance level. Rejecting H_0 implies that the similarity statistic between the test-affinity matrix at time't' and the reference affinity matrix (corresponding to 2 hours before seizure) is significantly different than the one obtained by randomly permuting the rows and columns of the test-affinity matrix. In Fig.1 the z_α scores in all seizures are almost always greater than z_{crit}. However, in a few instances, the z_α's exhibit a tendency to decrease gradually as the seizures approach. In a few other seizures, z_α's seem to have a negative bump that lasts for several minutes.

Reduced z_α's do not necessarily imply that the correlation estimates are small. However, verification of the original similarity statistic *r* indicated a reduced correlation estimate at those points corresponding to reduced z_α's. This observation directly suggests that the spatial relationships in the intracranial EEG data at those points are indeed very different (less correlated) from the spatial relationships observed around 2 hours prior to seizures.

As stated earlier, even though the z_α's show a remarkable decrease they are still greater than the z_{crit}. Also, notice that the absolute values of z_α's vary across seizures. These non-uniformities will render any comments regarding spatio-temporal changes prior to seizures, purely qualitative. It is therefore absolutely necessary to quantify the temporal decrease observed in correlation estimates. We propose a simple approach to statistically verify the decrease in the mantel statistics, z_α's.

The approach consists of checking whether the decreases observed in the Mantel test results (fig. 1) are statistically significant or not. Let z_{ref} be the reference z_α score at a time instance close to 2 hours before seizure. If $z_{t\_diff} = z_{t,\alpha} - z_{ref,\alpha}$, the null hypothesis H_0 can be stated as follows:

Null Hypothesis H_0: There is no difference in the z-scores, $z_{t,\alpha}$ and $z_{ref,\alpha}$.

The alternate hypothesis H_1: The z-scores $z_{t,\alpha}$ and $z_{ref,\alpha}$ are not equal.

Testing the hypothesis consists of the following steps:

1. Construct a distribution of z_α's from samples taken during inter-ictal states. Specifically, take any 2 hour segment from the background activity of the intracranial EEG data.

Construct affinity matrices as before and evaluate Mantel statistics to get z-scores. Repeat the above procedure on a number of such 2 hour segments (say 40) from background recording of the same patient and evaluate mantel test procedure for each one of them, to form an ensemble of z-scores, $z^i_{t,s}$ where t represents the time-index (hours), s represents the segment index (s = 1, 2, 3….., 40) and i is used to denote that these z-scores are computed on inter-ictal segments. For illustration, fig. 2 shows the smoothened z^i_α profiles corresponding to the inter-ictal segments. The smoothened z_α profile corresponding to seizure 1 is also shown superimposed on the z^i_α profiles.

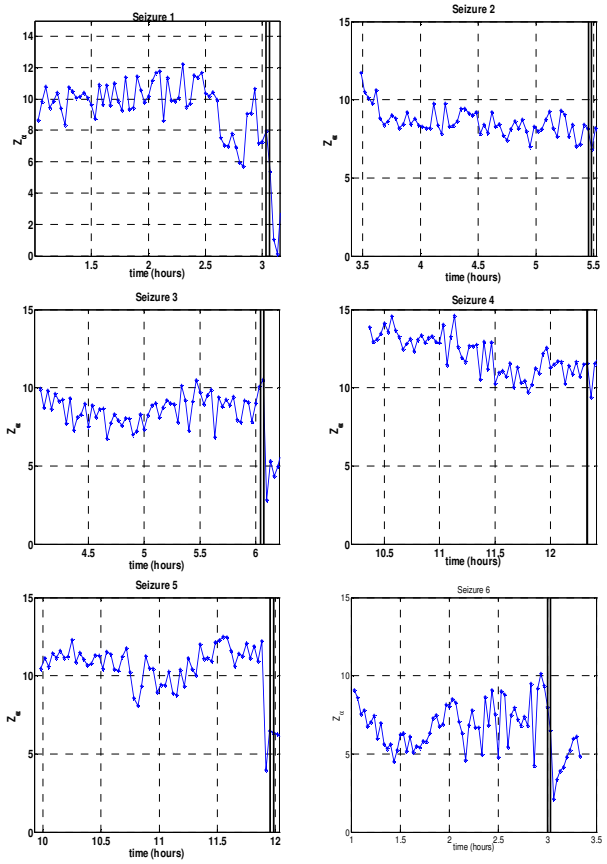

Figure 1. Quantifying the spatial changes along time using Mantel statistics. The vertical lines in the figure indicate seizure onset and termination periods. Notice that the statistical values show a slight decrease, approaching the seizures.

2. If $z^i_{t\_diff,s} = z^i_{ref,s} - z^i_{t,s}$ is the difference in the z-scores at time t relative to a reference time for the s_{th} segment, then $z^i_{t\_diff}$ forms a distribution that is constructed from all the 40 segments and is observed to be approximately Gaussian.

3. The idea is to check if the difference observed in the z-scores in the segment 2 hours before seizure (z_{t_diff}) is significantly different from the differences observed in the z-scores during inter-ictal states ($z^i_{t\_diff}$). We quantify this idea as follows:

$$Z_t = \frac{z_{t\_diff} - \bar{z}^i_{t\_diff}}{\sigma(z^i_{t\_diff})} \qquad (4)$$

where $z^i_{t\_diff}$ and $\sigma(z^i_{t\_diff})$ are the mean and variances of $z^i_{t\_diff}$, respectively. $Z_t > 1.96$ indicates the difference is significant and so the null hypothesis can be rejected at a 95% significance level. Since the test is one-tailed, the null hypothesis cannot be rejected if $Z_t < -1.96$. Even though it means that the differences are significant in those cases, a negative $z_{t\_diff} = z_{t,\alpha} - z_{ref,\alpha}$ implies an upward curve in fig 1 as the seizure is approached. Seizure 6 in fig. 1 can be one such instance.

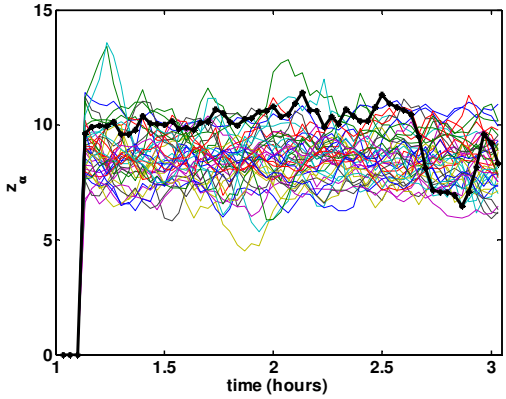

Figure 2. Time smoothened profiles of the Mantel statistics during inter-ictal states. The dark line shows the profile for seizure 1, patient P092.

Fig. 3 presents the Z_t scores as a function of time, for seizures 1 to 6 of the patient (P092). Z_t scores were computed for three different reference times. In other words, the z-scores at 90 minutes, 100 minutes and 110 minutes prior to a seizure were used as $z_{ref,\alpha}$. Fig. 3 shows profiles of Z_t scores for all the three reference times. Since we are particularly interested in Z_t scores > 1.96 (critical threshold), we make the following observations:

1. 5 out of the 6 seizures (the exemption being seizure 3) have clear time-instances where atleast one of the three Z_t scores are greater than the critical threshold.
2. The time-instances where critical thresholds are crossed vary from seizure to seizure.
3. The Z_t profiles corresponding to the three reference times (90, 100 & 110 minutes) are mostly consistent with respect to crossing the thresholds. Occasional discrepancies are seen, perhaps due to rapid fluctuations within the z-scores at reference times.

From the 1st observation above, we have clear evidence of spatial activity changes in the epileptic intracranial EEG data as the patient approaches seizure state. The 2nd observation tells us that the times at which the statistical changes are observed vary across seizures. This may indicate that the seizure markers in the form of spatio-temporal pattern changes, perhaps, are a complex function of the type of seizures and also the pathological state of the brain and possibly many other variables.

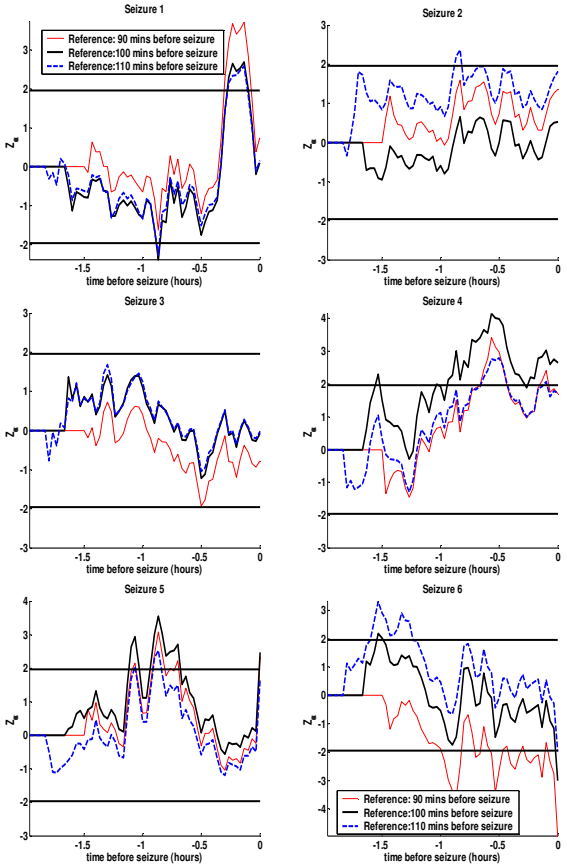

Figure 3. Illustrating the statistical difference between z-score at time 't' and z-score at a reference time, 90, 100 and 110 minutes before a seizure. Top to Bottom: profiles of z-score statistics for seizures 1 through 6 of patient P092.

IV. DISCUSSION

In this study, we propose a statistical analysis to quantify spatio-temporal changes in intracranial epileptic EEG. The Mantel statistics is a reasonably useful approach to distinguish pre-seizure patterns from those at inter-ictal stage of a seizure. So far, we have analyzed on a small set of seizures and the results have looked encouraging. Assuming distinct pre-seizure patterns exist; Mantel statistics analysis on a much larger set of seizures associated with different onset circumstances and in different patients may help us in finding the general sensitivity of this technique. There is also an ongoing debate on the existence of a pre-seizure state and the transition from inter-ictal state to pre-ictal state. The proposed analyses may serve as a step ahead in answering these issues.

ACKNOWLEDGMENT

This work is supported by NIH grant R01 NS 39687

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