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The Effect of Normalization of Partial Directed Coherence on the Statistical Assessment of Connectivity Patterns: A Simulation Study*

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Abstract— **Partial Directed Coherence (PDC) is a spectral multivariate estimator for effective connectivity, relying on the concept of Granger causality. Even if its original definition derived directly from information theory, two modifies were introduced in order to provide better physiological interpretations of the estimated networks: i) normalization of the estimator according to rows, ii) squared transformation. In the present paper we investigated the effect of PDC normalization on the performances achieved by applying the statistical validation process on investigated connectivity patterns under different conditions of Signal to Noise ratio (SNR) and amount of data available for the analysis. Results of the statistical analysis revealed an effect of PDC normalization only on the percentages of type I and type II errors occurred by using Shuffling procedure for the assessment of connectivity patterns. No effects of the PDC formulation resulted on the performances achieved during the validation process executed instead by means of Asymptotic Statistic approach. Moreover, the percentages of both false positives and false negatives committed by Asymptotic Statistic are always lower than those achieved by Shuffling procedure for each type of normalization.**

I. INTRODUCTION

Effective connectivity between cerebral areas is defined as the temporal correlation between spatially remote neurophysiologic events and it could be estimated by using different methods both in time as well as in frequency domain based on bivariate or multivariate autoregressive models (MVAR) [1]–[3].

Methodologies, such as Directed Transfer Function (DTF) [2] or Partial Directed Coherence (PDC) [3], defined in frequency domain and based on multivariate approach have been demonstrated to be more efficient in estimating effective connectivity. In fact the bivariate approach is affected by a high number of false positives due to the impossibility of the method in discarding a common effect on a couple of signals of a third one acquired simultaneously [4]. Among the multivariate spectral estimators, the PDC technique [3] is also of particular interest for several neuroscientific applications. In fact it allows to distinguish between direct and indirect connectivity flows in the estimated connectivity pattern better than DTF and its direct modified version, the dDTF [5].

Even if the original definition of the PDC estimator derived directly from information theory, its formulation was modified in order to give a better physiological interpretation to the estimation results achieved on electrophysiological data. In particular, a new type of normalization, already used for DTF was introduced by dividing each estimated value of PDC for the root squared sums of all the elements of the relative row in order to avoid emphasis on the sinks of information due to column normalization. Moreover, in order to put the estimator directly in relation with the power density of the signals included in the process, a squared version has been introduced.

The higher performances of squared PDC methods in respect to plain PDC have been already demonstrated in a simulation study which revealed its higher accuracy in the estimation of connectivity patterns on data characterized by different lengths and SNR and in distinction between direct and indirect paths [6]. Even if the new type of normalization has been introduced several years ago, a complete characterization of its effects on the accuracy of estimated networks has not been provided yet.

For this reason, in the present paper, we proposed a simulation study aiming at the evaluation of the effects of the normalization on the performances achieved by applying the statistical validation process on estimated patterns, under different conditions of SNR and amount of data available for the analysis. In particular we used different sets of simulated data reproducing a predefined connectivity scheme. The assessing methods included in the study were the shuffling approach and the more recent asymptotic statistic method. The evaluation of performances was performed on the percentages of false positives and false negatives occurred during the validation process.

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II. Methods

A. Partial Directed Coherence

The PDC [3] is a full multivariate spectral measure, used to determine the directed influences between pairs of signals in a multivariate data set. This estimator was demonstrated to be a frequency version of the concept of Granger causality [7]. It is possible to define PDC as

$$\pi_{ij}^{col}(f) = \frac{\Lambda_{ij}(f)}{\sqrt{\sum_{k=1}^{N} \Lambda_{kj}(f)\Lambda_{kj}^{*}(f)}} \quad (1)$$

where $\Lambda_{ij}(f)$ represents the coefficient ij of the matrix of parameters in MVAR models, transformed in frequency domain.

Even if this formulation derived directly from information theory, the original definition was modified in order to give a better physiological interpretation to the estimate results achieved on electrophysiological data. In particular, a new type of normalization, already used for DTF was introduced. Such normalization consisted in dividing each estimated value of PDC for the root squared sums of all elements of the relative row, obtaining the following definition:

$$\pi_{ij}^{row}(f) = \frac{\Lambda_{ij}(f)}{\sqrt{\sum_{k=1}^{N} \Lambda_{ik}(f)\Lambda_{ik}^{*}(f)}} \quad (2)$$

Moreover, a squared formulation of PDC has been introduced and can be defined as follows for the two types of normalization:

$$sPDC_{ij}^{col}(f) = \frac{\left|\Lambda_{ij}(f)\right|^2}{\sum_{k=1}^{N} \left|\Lambda_{kj}(f)\right|^2} \quad (3)$$

$$sPDC_{ij}^{row}(f) = \frac{\left|\Lambda_{ij}(f)\right|^2}{\sum_{k=1}^{N} \left|\Lambda_{ik}(f)\right|^2} \quad (4)$$

The main difference with respect to the original formulation is in the interpretation of these estimators. Squared PDC can be put in relationship with the power density of the investigated signals and can be interpreted as the fraction of i^{th} signal power density due to the j^{th} measure. The higher performances of squared methods in respect to simple PDC have been already demonstrated in a simulation study [6].

B. Statistical Assessment of Connectivity Patterns

Random correlation between signals induced by environmental noise or by chance can lead to the presence of spurious links in the connectivity estimation process. In order to assess the significance of estimated patterns, the value of effective connectivity for a given pair of signals and for each frequency, obtained by computing PDC, has to be statistically compared with a threshold level which is related to the lack of transmission between considered signals.

Different approaches are actually available for reconstructing the null-case PDC distribution to be used in the statistical validation process. In this study we considered two among them: i) Shuffling procedure and ii) Asymptotic Statistic method. The Shuffling approach is a time-consuming procedure which allows to reconstruct the PDC distribution in the null case by means of an empirical data-driven process. It consists in iterating the PDC estimation on different surrogate data sets obtained by shuffling the original traces in order to disrupt the temporal relations between them [8]. Recently, a new approach based on the theoretical distribution of null-case PDC was introduced. Such Asymptotic Statistic method derived from the assumption that PDC estimator for the not-null hypothesis is asymptotically normally distributed, while it tends to a χ^2-distribution in the null case [9], [10]. Thus, the null-case distribution of PDC is derived from the acquired signals by applying a Monte Carlo method able to reshape the data on a χ^2-distribution to be used in the assessment process. Details about the method can be found in Takahashi et al. [10].

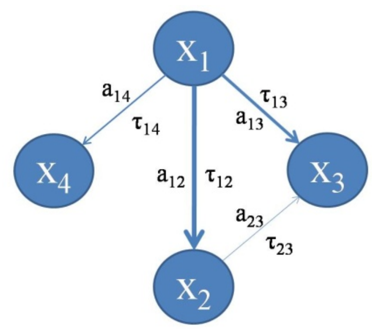

Fig. 1 – Connectivity model imposed in the generation of testing dataset. x1,…, x4 represent the signals of four cerebral regions of interest. a_{ij} and τ_{ij} represent the strength of the imposed connection the delay in transmission applied between nodes i and j. The values chosen for connections strength are a_{12}=0.5, a_{13}=0.4 a_{14}=0.2, a_{23}=0.08, while the values set for delays in transmission are τ_{12}=10s, τ_{13}=10s, τ_{14}=5s, τ_{23}=20s at sampling rate of 200Hz. The chosen values are those typical of EEG signals.

The statistical validation process has to be applied on each couple of signals for each direction and for each frequency sample. This necessity leads to the execution of a high number of simultaneous univariate statistical tests with evident consequences in the occurrence of type I errors. The statistical theory provides several techniques that could be usefully applied in the context of the assessment of connectivity patterns in order to avoid the occurrence of false positives. In this study we considered the traditional Bonferroni approach [11] and the recently introduced False Discovery Rate criterion [12].

C. The Simulation Study

The simulation study was composed by the following steps:

1) Generation of several sets of test signals simulating activations at scalp or cortical levels. These datasets were generated in order to fit a predefined connectivity model reported in Fig.1 and to respect imposed levels of some factors. These factors were the SNR (factor SNR: 0.1, 1, 3, 5, 10) and the total length of the data (factor LENGTH: 15s,

50s, 100s, 150s). The chosen values are those typical of EEG recordings.

2) Estimation of the cortical connectivity patterns obtained in different conditions of SNR and data LENGTH by means of $sPDC^{col}$ (squared PDC normalized according to columns), $sPDC^{row}$ (squared PDC normalized according to rows) and $sPDC^{nn}$ (squared PDC not normalized). The normalization was applied before and after the validation process (factor TYPENORM: NN (not normalized), NRB (normalization according to rows before validation), NRA (normalization according to rows after validation), NCB (normalization according to columns before validation), NCA (normalization according to columns after validation)).

3) Application of shuffling and asymptotic statistic procedures for assessing significance of estimated connectivity patterns for a significance level of 5% in three different cases: no correction, corrected for multiple comparisons by means of False Discovery Rate (FDR) and Bonferroni adjustments (factor CORRECTION).

4) Computation of the total percentage of false positives and false negatives occurred in the assessment of significance of connectivity patterns for all the considered factors.

5) Statistical analysis on percentage of both false positives and negatives by means of ANOVA for repeated measures in order to evaluate the effects of some factors (SNR, LENGTH, CORRECTION, NORMTYPE) on the performances achieved by means of the two validation methods separately.

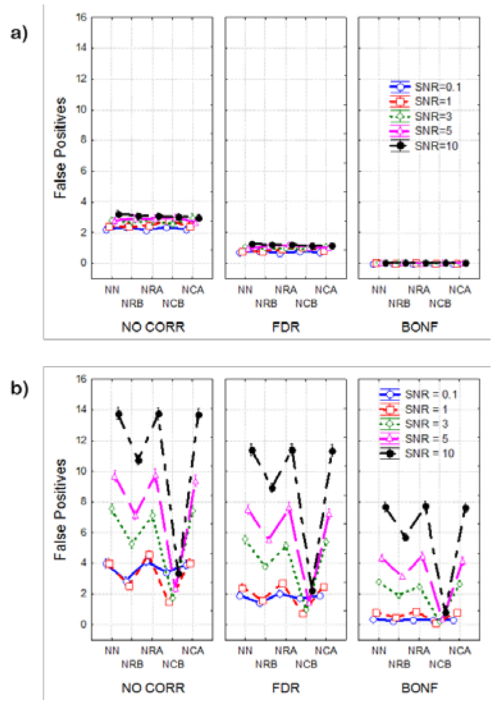

Fig. 2 – Results of the ANOVA analysis computed considering as dependent variable the percentage of False Positives occurred during the assessment process computed by means of Asymptotic Statistic method (panel a) and Shuffling procedure (panel b). Plot of means with respect to the interaction between SNR, CORRECTION and NORMTYPE factors.

III. RESULTS

A MVAR model of order 16 was fitted to each set of simulated data. The procedure of signal generation and PDC estimation was repeated 100 times for each level of factors SNR, LENGTH, NORMTYPE and CORRECTION in order to increase the robustness of the following statistical analysis.

Results of four-way ANOVA computed by setting as dependent variable the percentage of false positives revealed a strong statistical influence of the main factors SNR ($F = 46.92$, $p < 0.0001$), LENGTH ($F = 111.57$, $p < 0.0001$), and CORRECTION ($F=12685$, $p<0.0001$), as well as their interactions SNR x LENGTH ($F=6.38$, $p<0.0001$), SNR x CORRECTION ($F=36$, $p<0.0001$), LENGTH x CORRECTION ($F=91$, $p<0.0001$) on the percentages of false positives occurred during the statistical assessment performed by means of Asymptotic Statistic. No effects of the factor NORMTYPE and its interactions with other factors were highlighted by the ANOVA analysis as confirmed by Fig.2a and Fig 3a.

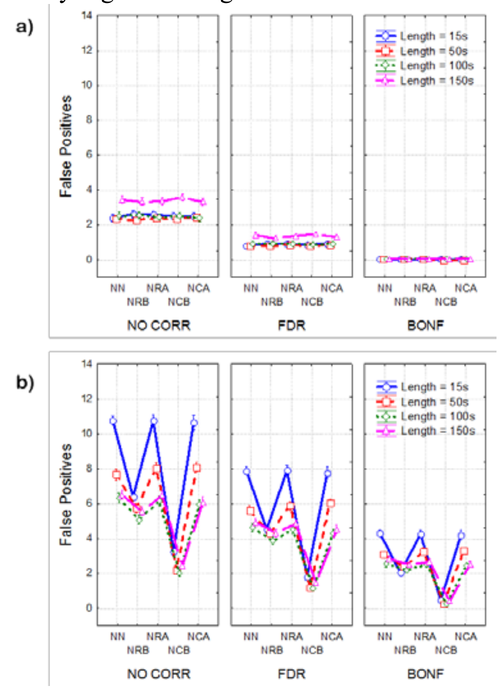

Fig. 3 – Results of the ANOVA analysis computed considering as dependent variable the percentage of False Positives occurred during the assessment process computed by means of Asymptotic Statistic (panel a) and Shuffling (panel b). Plot of means with respect to the interaction between LENGTH, CORRECTION and NORMTYPE factors.

In particular we reported the results of the ANOVA analysis performed on the percentages of false positives committed by Asymptotic Statistic approach. In particular we reported plot of means with respect to the interaction between SNR, CORRECTION and NORMTYPE factors in Fig.2a and LENGTH, CORRECTION and NORMTYPE factors in Fig.3a. The percentages of false positives remained below 5% for all the normalization types, all the SNR, data length and corrections. In particular we found a decrease of such percentage related to the decrease of SNR and to the increase of Data Length and severity of the correction for multiple comparisons. No differences between the different types of normalization were highlighted.

Results of four-way ANOVA computed by setting as dependent variable the percentage of false positives revealed a strong statistical influence of the main factors NORM (F =

1232, $p < 0.00001$), SNR ($F = 3245.8$, $p < 0.0001$), LENGTH ($F = 402.62$, $p < 0.0001$), and CORRECTION ($F=23756$, $p<0.0001$), as well as their interactions NORM x SNR ($F = 169.21$, $p < 0.00001$), NORM x LENGTH ($F = 47.05$, $p < 0.00001$), SNR x LENGTH ($F=10.4$, $p<0.0001$), NORM x CORRECTION ($F=427.46$, $p<0.0001$) on the percentages of false positives occurred during the statistical assessment performed by means of Shuffling procedure.
In Fig.2b and Fig.3b we reported the results of the ANOVA analysis performed on the percentages of false positives occurred by applying Shuffling procedure. In particular we reported plot of means with respect to the interaction between SNR, CORRECTION and NORMTYPE factors in Fig.2b and LENGTH, CORRECTION and NORMTYPE factors in Fig.3b. In this case the percentages of false positives are higher in respect to those achieved by Asymptotic Statistic approach. However they decreased with the decrease of SNR and with the increase of data length and of the severity of corrections for multiple comparisons. Both panels revealed an effect of the normalization type on the percentages of false positives. Duncan's pairwise comparisons highlighted differences between the normalization performed after the validation process in respect to the one executed before in both rows and columns cases. In particular the normalization performed before validation process led to lower percentages of false positives in respect to all the others normalization as revealed in Fig.2b and Fig.3b.

Similar behavior was found for the percentages of false negatives. Details about the results achieved were not reported due to the brevity of the paper. However, the percentages of false negatives were not influenced by the normalization type in the Asymptotic Statistic case. Instead significant effects of factor NORMTYPE on the percentages of false positives was found in Shuffling case. The higher percentages of false negatives were found for NRB and NCB cases.

IV. DISCUSSION

All the results described in this paper highlighted some important factors affecting the statistical validation process. In particular, the percentages of false positives are strongly influenced by the quality of data included in the estimate as already demonstrated in [6], [13]. In fact the percentages of false positives decreased for decreasing values of SNR and increasing values of Data Length. An opposite behavior was found for the percentages of false negatives. Also the effect of different types of correction for multiple comparisons was in agreement with previous findings [13]. The decrease of false positives and the correspondent increase of false negatives were related to the severity of adjustment for multiple comparisons. The comparison between the two validation approaches confirmed the role of Asymptotic Statistic as a valid alternative to the time consuming Shuffling procedure [13] due to its higher performances under different conditions of data quality.

The definition of PDC estimator affected only the percentages of type I and type II errors occurred by using Shuffling procedure. In particular for normalization according to rows and columns both before the validation process resulted low percentages of false positives and high percentages of false negatives. No effects of the PDC formulation resulted on the performances achieved during the validation process executed by means of Asymptotic Statistic.

V. CONCLUSION

Results showed in the present paper provided some guidelines for the use of normalizations to be applied to PDC estimator in relation to the quality of data available for the analysis and to the method used for the statistical validation process. Moreover, the simulation study not only confirm the higher performances of Asymptotic Statistic method in preventing both type I and type II errors but also highlighted its independence from the type of normalization used for PDC estimator.

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