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A New Statistical Approach for the Extraction of Adjacency Matrix from Effective Connectivity Networks*

J. Toppi, F. De Vico Fallani, M. Petti, G. Vecchiato, A. Maglione, F. Cincotti, S. Salinari, D. Mattia,

F. Babiloni, L. Astolfi

Abstract— **Graph theory is a powerful mathematical tool recently introduced in neuroscience field for quantitatively describing the main properties of investigated connectivity networks. Despite the technical advancements provided in the last few years, further investigations are needed for overcoming actual limitations in the field. In fact, the absence of a common procedure currently applied for the extraction of the adjacency matrix from a connectivity pattern has been leading to low consistency and reliability of ghaph indexes among the investigated population. In this paper we proposed a new approach for adjacency matrix extraction based on a statistical threshold as valid alternative to empirical approaches, extensively used in Neuroscience field (i.e. fixing the edge density). In particular we performed a simulation study for investigating the effects of the two different extraction approaches on the topological properties of the investigated networks. In particular, the comparison was performed on two different datasets, one composed by uncorrelated random signals (null-model) and the other one by signals acquired on a mannequin head used as a phantom (EEG null-model). The results highlighted the importance to use a statistical threshold for the adjacency matrix extraction in order to describe the real existing topological properties of the investigated networks. The use of an empirical threshold led to an erroneous definition of small-world properties for the considered connectivity patterns.**

I. Introduction

The methodological advancements in the field of effective connectivity allow today the description of neurological mechanisms at the basis of complex cerebral processes involving a large number of sources. Once qualitatively described the connectivity pattern achieved for the investigated condition, a quantitative characterization of its main properties is necessary in order to synthetize the huge amount of information derived from the application of such advanced methodologies.

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J. Toppi (Corresponding Author. Phone: +39 06 51501510; e-mail: jlenia.toppi@uniroma1.it), M. Petti, F. Cincotti, L. Astolfi are with the Department of Computer, Control, and Management Engineering, Univ. of Rome "Sapienza" and with Fondazione Santa Lucia Hospital, Rome, Italy.

D. Mattia is with Fondazione Santa Lucia Hospital, Rome, Italy.

S. Salinari is with the Department of Computer, Control, and Management Engineering, Univ. of Rome "Sapienza", Rome, Italy.

G. Vecchiato and F. Babiloni are with the Dept. of Physiology and Pharmacology of the University of Rome "Sapienza" and with Fondazione Santa Lucia Hospital, Rome, Italy.

A.G. Maglione is with Department of Anatomy, Histology, Forensic Medicine and Orthopedics, University of Rome, "Sapienza" and with Fondazione Santa Lucia Hospital, Rome, Italy.

The use of salient indexes describing important features of brain connectivity patterns has been revealed as important for the interpretation, comparison and statistical analysis of functional networks. However, such challenging topic needs to be improved and refined in order to be performed in a consistent, stable and repetitive way.

In the last ten years, a graph theoretical approach was proposed for the characterization of the topological properties of real complex networks [1]. The process of graph indexes extraction is based on the definition of an adjacency matrix describing the structure of the investigated network. The methodologies currently available for adjacency matrix extraction consist in a comparison between the connectivity matrix and a threshold usually defined in empirical way. Such empirical criteria, which often modify the topological structure of the network, could highly affect the properties of investigated patterns [2]. In particular, four criteria are typically adopted: i) an arbitrary threshold, to discard the weak connections [3]; ii) the largest possible threshold that allows all nodes to be connected at least to another node in the network [4]; iii) fixing the average degree within the networks in order to maximize the small-world properties of the network [5]; iv) fixing the edge density of the network, i.e. the number of existing edges divided by the number of possible edges [5].

In the present paper we aim at investigating the effects of adjacency matrix extraction procedures on the interpretation of graph theory indices as descriptors of the global and local properties of considered networks. The objective was to define a reliable approach for the derivation of salient indices from connectivity networks estimated by means of multivariate methods. In particular we used two different datasets, modeling the ideal and the experimental null-case connectivity conditions, with the purpose of comparing one of the methods extensively used in graph theory applications for extracting adjacency matrices from the connectivity patterns (i.e. the method based on fixing the edge density) with the new proposed method based on the thresholds extracted by means of the statistical validation of connectivity patterns [6].

II. Methods

A. Partial Directed Coherence

The PDC [8] is a full multivariate spectral estimator, used to describe the directed influences between any given pair of signals in a multivariate data set. This estimator was demonstrated to be a frequency version of the concept of Granger causality [9].

It is possible to define PDC ($\pi_{ij}(f)$) as:

$$\pi_{ij}(f) = \frac{\Lambda_{ij}(f)}{\sqrt{\sum_{m=1}^{N} \Lambda_{mj}(f)\Lambda_{mj}(f)}} \quad (1)$$

where $\Lambda_{ij}(f)$ is the (i,j) entry of the connectivity matrix Λ containing the frequency version of the associated Multivariate Autoregressive (MVAR) model coefficients and N represents the number of signals included in the estimate.

In this study we used the square formulation of PDC [7] due to its higher accuracy and stability.

B. Statistical Assessment of Connectivity Estimates: Shuffling Procedure

The investigated connectivity patterns have to be statistically validated in order to discard all the spurious links due to random correlation between signals included in the estimation process. In order to assess the significance of estimated patterns, the values of effective connectivity should be statistically compared with a threshold level which represents the lack of communication between the considered nodes. The shuffling is a time consuming procedure, introduced in 2001, which allows to achieve null-case distribution by iterating the PDC estimation on different surrogate data sets obtained by shuffling the phases of original traces in order to disrupt the temporal relations between them [8]. The simultaneous execution of univariate statistical tests, one for each couple of nodes, for each direction and frequency sample, led to the necessity to introduce corrections for multiple comparisons in the significance level imposed in validation process. In this study we used the False Discovery Rate (FDR), whose higher performances in discarding both false positives and false negatives have been already demonstrated [9].

C. Graph Theory

A graph is a mathematical object consisting in a set of vertices (or nodes) linked by means of edges (or connections) indicating the existence of information flows between the considered nodes. Graph structure is fully described by means of an adjacency matrix *G:*

$$G_{ij} = \begin{cases} 1 \rightarrow \Lambda_{ij} \geq \tau \\ 0 \rightarrow \Lambda_{ij} < \tau \end{cases} \quad (2)$$

where Λ_{ij} represents the connectivity matrix and τ the empirical or statistical threshold used for the process. Several indices based on the elements of such matrix can be extracted for the characterization of the main properties of investigated networks.

Characteristic Path Length. The characteristic path length is the average shortest path length (i.e. minimum number of edges that link one node to another) in the network. It can be defined as follows

$$L = \frac{1}{N}\sum_{i \in N} L_i = \frac{1}{N}\sum_{i \in N} \frac{\sum_{j \in N, j \neq i} d_{ij}}{N-1} \quad (3)$$

where L_i is the average distance between node i and all other nodes and d_{ij} is the distance between node i and node j.

Clustering Coefficient. The clustering coefficient describes the density of interconnections between the neighbors of a node [10]. It is defined as the fraction of triangles around a node or the fraction of node's neighbors that are neighbors of each other. The binary directed version of Clustering Coefficient is defined as follows [11]:

$$C = \frac{1}{N}\sum_{i \in N} C_i = \frac{1}{N}\sum_{i \in N} \frac{t_i}{(k_i^{out} + k_i^{in})(k_i^{out} + k_i^{in} - 1) - 2\sum_{j \in N} G_{ij} G_{ji}} \quad (4)$$

where t_i represents the number of triangles involving node i, k_i^{in} and k_i^{out} are the number of incoming and outcoming edges of nodes i respectively and g_{ij} is the entry ij of adjacency matrix.

Small-Worldness. A network G is defined as small-world network if $L_G > L_{rand}$ and $C_G >> C_{rand}$ where L_G and C_G represent the characteristic path length and the clustering coefficient of a generic graph and L_{rand} and C_{rand} represent the correspondent quantities for a random graph [10]. On the basis of this definition, a measure of small-worldness of a network can be introduced as follows

$$S = \frac{C_G / C_{rand}}{L_G / L_{rand}} \quad (5)$$

So a network is said to be a small-world if S > 1 [12] .

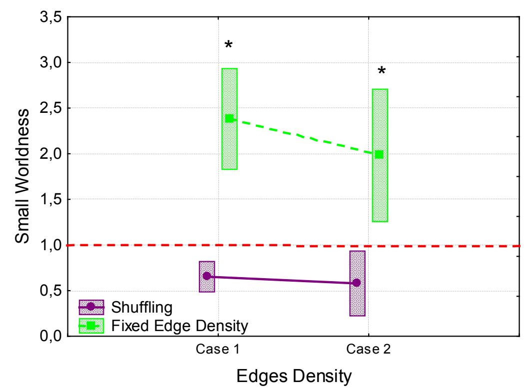

Figure 1. Results of ANOVA performed on the Small-Worldness Index computed on networks inferred from simulated data, using METHOD and EDGE as within main factors. The green dotted line represents the threshold above which a network is said to be "small-world". The symbol (*) indicates a statistical difference between shuffling procedure and fixed edge density method, highlighted by Tukey's post hoc test (p<0.05).

D. Description of the Study

Two datasets were used in the study: i) "simulated data" composed by random signals completely uncorrelated among each other; ii) "mannequin data", achieved by simulating an EEG recording on a head of a synthetic mannequin by using a 61-channel system. The two datasets represented a null model for connectivity estimator in ideal case and during experimental condition respectively. In fact, the absence of physiological content in the signals recorded on mannequin allows modeling the absence of information flows between electrodes, but at the same time, the use of a real EEG cap, with electrodes positioned as 10-20 systems and references placed at the earlobes, models the effects of some factors typical of an EEG recording situation (electrodes and ground position, monitor interference, environmental noise).

Both datasets were subjected to the following signal processing procedure:

1) Effective Connectivity estimation by means of PDC

2) binary adjacency matrix extraction by means of threshold τ achieved in two different ways:

- by shuffling procedure for a significance level of 5% in two conditions: i) not corrected for multiple comparisons (Case 1) and ii) adjusted for multiple comparisons by False Discovery Rate (Case 2).
- by fixing the edge density k to predefined values. The levels of such values were chosen equal to those achieved by the shuffling procedure, to avoid different performances between the two methods due to the selection of a different density of edges.

3) Extraction of the Small-Worldness (SW) index from the adjacency matrices achieved with both methodologies

Such procedure was repeated 50 times in order to increase the power of the following statistical test (ANOVA) computed for comparing the two approaches used for the extraction of the adjacency matrices. In particular we computed a two-way ANOVA considering the *SW* index as dependent variable. The main factors were the method used for extracting adjacency matrices (METHOD: Shuffling and Fixed Edge Density procedures) and the edge density (EDGE: Case 1 and Case 2). The ANOVA was applied separately to both simulated and mannequin data.

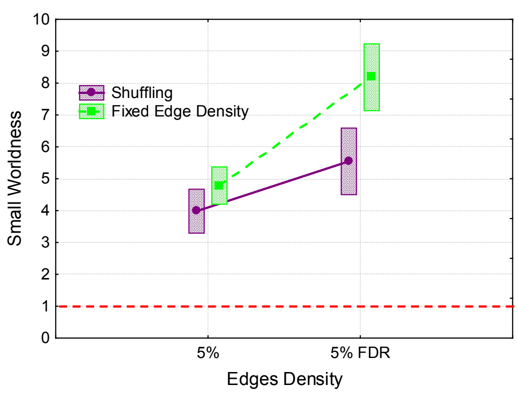

Figure 2. Results of ANOVA performed on the Small-Worldness Index computed on networks inferred from mannequin data using METHOD and EDGE as within main factors. The red dotted line represents the threshold above which a network is said to be "small-world". The symbol (*) indicates a statistical difference between shuffling procedure and fixed edge density method, highlighted by Tukey's post hoc test (p<0.05).

III. Results

Results of ANOVA revealed statistical influence of the factors METHOD (p<0.00001, F=34.87) and METHOD x EDGE (p<0.00001, F=13.46) on the *SW* index computed on connectivity networks inferred from simulated data. In Fig.1 we reported the correspondent results. In particular we showed the plot of means with respect to the interaction between METHOD and EDGE factors. Fig.1 highlighted that the use of the method based on a fixed edge density revealed "small-world" properties of the network obtained from uncorrelated signals, for both density values (S>1). On the contrary, the application of the shuffling procedure allowed to correctly identify the absence of small-worldness in the network (S<1). Such results were confirmed by Tukey's pairwise comparisons.

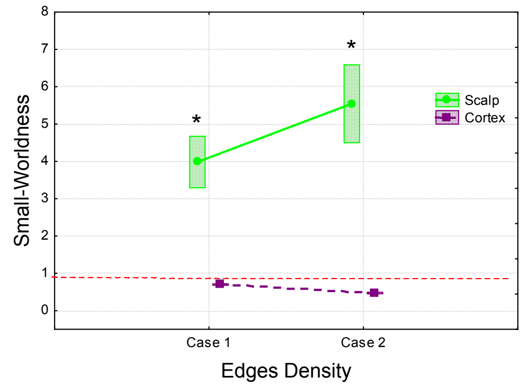

Figure 3. Results of ANOVA performed on the Small-Worldness Index computed on networks inferred from mannequin data at scalp and cortical levels, using LEVEL and EDGE as within main factors. The adjacency matrix was extracted by means of shuffling procedure. The red dotted line represents the threshold above which a network is said to be "small-world". The symbol (*) indicates a statistical difference between estimates provided at scalp and cortical levels, highlighted by Tukey's post hoc test (p<0.05).

Results revealed statistical influence of the main factors METHOD (p=0.0001, F=23.42), EDGE (p<0.00001, F=104.47) and METHOD x EDGE (p=0.00021, F=15.99) on the SW index computed on connectivity networks inferred from mannequin data. The findings were reported in Fig.2. In particular the statistical analysis revealed small-world properties in the investigated networks for both methodologies and both edges density. Higher values for Fixed Edge Density in respect to Shuffling procedure resulted in Case 2 as confirmed by Tukey's pairwise comparisons.

In order to understand if the small-world properties of the investigated networks depend on the correlations between neighboring electrodes or from the position of the reference, we move the analysis from scalp to cortical level. In particular we used an advanced methodology for electrical sources reconstruction, the Weighted Minimum Norm, to project the data acquired at scalp level from the mannequin head to the space of sources [13]. This process allows to delete all the correlations due to volume conduction effect. The corresponding cortical waveforms, achieved for regions of interests selected by chance, were subjected to the same analysis of scalp signals. Then in order to compare the two conditions, we performed an ANOVA considering as dependent variable the *SW* index and as within main factors the level at which the analysis was executed (LEVEL: scalp or cortex) and the edge density (EDGE: Case 1 and Case 2).

Results of the statistical analysis revealed influence of the main factors LEVEL (p<0.00001, F=98.24), EDGE (p<0.00001, F=31.04) and LEVEL x EDGE (p<0.00001, F=55.66) on the *SW* index computed on connectivity networks inferred from mannequin data. The adjacency matrix was extracted by means of shuffling procedure. In Fig.3 we reported the correspondent results. In particular we showed the plot of means with respect to the interaction between LEVEL and EDGE factors. Results reported in Fig.3 showed how the *SW* index computed on networks inferred from data reconstructed at cortical level remained below 1 for the two edges density, confirming the hypothesis that the small-world properties at scalp level are mainly associated to correlations between neighboring electrodes.

IV. Discussion

In the present study we made a comparison between one of the methods extensively used in graph theory applications for extracting adjacency matrices from the connectivity patterns (i.e. the method based on fixing the edge density) and the shuffling procedure in order to describe the effects of the modalities for adjacency matrix extraction on the "small world" properties of the network.

The results achieved on simulated data revealed that the use of the empirical criterion leads to erroneous definition of small-world properties of the network, independently from the edge density chosen. In fact, the simulated data, being uncorrelated, should produce connectivity patterns without any topological properties of small-worldness. This means that the shuffling procedure doesn't just preserve the strongest connections as the fixed edge density criterion and thus the significance of a link is not merely related to its strength. For this reason a statistical validation, combined with multiple comparisons adjustments, is necessary in order to extract graph measures able to describe the real properties of the considered network.

The results achieved on mannequin data showed small-world properties of the networks extracted by applying both methodologies. In this case, the shuffling procedure couldn't prevent the description of mannequin networks as small world networks. This effect could be explained with the existence of real correlations between electrodes, which can occur in real EEG data, due to volume conduction effect and to the location of the reference [14]. Such hypothesis is confirmed by the fact that the application of shuffling approach on data reconstructed at cortical level led to a correct definition of topological properties of investigated networks (no small-world properties). In fact the procedure used for reconstructing cortical sources worked as spatial high-pass filter, deleting all the correlations between neighboring electrodes. Thus *SW* index cannot be considered as an absolute measure, because its value contains some of the real correlations due to neighboring electrodes. At scalp level only variations of this measure between two conditions within the same subject, or between two subjects in the same conditions can be computed, in order to discard all the effects due to the position of the electrodes on the scalp.

V. Conclusion

All the results reported in the present paper highlighted the necessity to use a validation process for extracting the threshold to be used for adjacency matrix extraction. In fact this approach is necessary to avoid erroneous definition of topological properties of the investigated networks.

Moreover a new definition of the concept of small-worldness is provided due to its strong dependence from correlations between neighboring electrodes. At scalp level it could be used only for describing variations between two conditions. As absolute value, *SW* index can be used only after removing the source of correlation.

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