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Analysis of fMRI Data using the Complex Systems Approach

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Abstract – **Physiological and biological systems can be characterized as complex processes whose dynamics are constantly being influenced by nonlinear interactions. The outputs of these systems correspond to different modes of reaction due to dynamic relationships that are established between components of the system, perturbations from the external environment and changes that occur at physiological levels in the body. In this work, recent advances in the field of nonlinear dynamics are applied to fMRI data to examine the spatio-temporal properties of BOLD signal during a working memory task completion. Two groups of human subjects, one affected by schizophrenia and healthy controls, were imaged during the task completion. Recurrence properties were extracted from the time series of the most relevant voxels, using the Recurrence Plots (RP) and the Recurrence Quantitative Analysis (RQA). The purpose of the paper is to perform a description of the functional states, as well as to capture differences (if any) between the groups. Results are still preliminary but the methodology applied has margin of improvements.**

I. INTRODUCTION

Neuroscientists, in the last twenty years, have learned a lot about the spatio-temporal nature of brain function through functional connectivity studies using various statistical approaches, including linear correlations between spatial regions [15], data-driven methods [4] and, recently, applying nonlinear analysis [9]. Linear methods make the underlying assumption that the signals are produced by a linear stochastic system. Arguments based on brain physiology, however, suggest that the brain may be better modeled as a nonlinear complex system. So, while linear approach works to a certain extent because a linear system can always approximate the behavior of a nonlinear system, nonlinear approaches may be more pertinent and sensitive, revealing additional insights into the brain nature. In details, literature focused on the research and description of the specialized functional areas and the understanding of their integration in different conditions: mental diseases, completion of tasks, emotional or cognitive status.

Among the available medical imaging techniques, the most used to investigate the brain activity is the functional Magnetic Resonance Imaging (fMRI). fMRI captures the blood-oxygen-level dependent (BOLD) signal, which is closely connected to the hemodynamic response of neuronal metabolic activity [14]. The fMRI technique has shown to be a powerful tool to understand the brain connectivities through the monitoring of the brain activity while administering a task condition. It is noninvasive, does not involve radiations and has high spatial resolution and moderate temporal resolution.

Although a large effort has been already done in the modeling of the BOLD response as a function of the neuronal activity [20, 8, 3], very little work has been done in applying methods of nonlinear dynamics on fMRI data. Previous studies of nonlinear dynamics, in fact, deal about EEG [19], where the number of time series is considerably lower and the time resolution higher.

Our general idea is to consider the fMRI data as the emergent description of a nonlinear dynamic system evolving in time, at least for a part of the brain. The system evolution is supposed to be described by a set of nonlinear differential equations of hidden variables [18]. In this paper we give up to accurately describe the phase state or to solve such equations; instead, we want to infer general nonlinear properties of the systems due to the time evolution of such variables. The representation of variables evolution, in a proper hyperspace, is a manifold. The description of the properties of such manifold, with the aim of describing the brain nature, functioning and reaction to cognitive processes, external stimuli or diseases, is the ultimate purpose of this line of research started with EEG [10, 16].

To model this manifold we resort to the concept of *recurrence*, a fundamental property of nonlinear dynamical systems, used to characterize the system's behavior in the phase space. The main concepts of recurrence derive since the Poincare' Recurrence theorem and can qualitatively be summarized in the following two properties: (i) similar situations often evolve in a similar way, (ii) some situations occur over and over again.

A powerful tool for the visualization and analysis of nonlinear systems is the recurrence plot (RP) [7, 12], a tool used to visualise the recurrences of dynamical systems. The recurrence quantification analysis (RQA) is the consequent quantification of some nonlinear measurements done

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on the recurrence plots. RQA measures can be put in relation with the invariant parameters that characterize a nonlinear system, as the correlation dimension, the topological entropy, the Lyapunov exponents. RP and RQA have found extensive applications in economy, physiology, neuroscience, Earth sciences, climatology, astrophysics and engineering [12].

In this paper preliminary results are shown on RQA measures extracted from fMRI data, together with the methodology adopted to highlights the complex nature of such quantities.

II. GENERAL FRAMEWORK

The RP–RQA analysis has been used as the framework to characterize specific brain areas of altered states or significant neuronal activation differences as consequence of a mental disease.

A. *Experimental Setting*

9 patients suffering from schizophrenia and 9 healthy control subjects have performed an alternating block task paradigm, consisting of a visual-motor condition and a working memory (WM) condition, the visual N-back WM task [2]. A gradient echo BOLD echo-planar imaging pulse sequence has been used to acquire 120 images, one every 2 sec. Each functional image consists of 20×6 mm thick axial slices covering the entire cerebrum and most of the cerebellum (matrix=64×64 pixel for each slice). Data have been preprocessed using the SPM8 software package (http://www.fil.ion.ucl.ac.uk/spm/). Images for each subject were aligned to the first volume in the time series to correct for head motion, spatially normalized into a standard space and smoothed by a 10 mm isotropic 3D Gaussian kernel (more details in [13]).

The implied hypothesis of the proposed indicator is that healthy subjects and schizophrenic patients may be discriminated on the basis of the different activation areas or, more subtly, different behavior of the estimated nonlinear features, as already demonstrated for epileptic seizure in EEG [18]. In the case of schizophrenia, this analysis is justified by the physiological origin of the disease (the Dopamine Hypothesis [11]) that correlates the negative and cognitive symptoms especially with the transient phases, when the subject is requested to promptly change his/her state from rest to activity [5].

B. *Statistics and Nonlinearity Tests*

The algorithm block scheme is represented in Fig. 1.

The first question we tried to answer was: is the BOLD really expression of a nonlinear system? If so, the time series should provide positive result to any nonlinearity test. Another question concerns the degree of stochasticity of the time evolution (i.e. how much measures are prone to be described by statistical tool instead of deterministic equations).

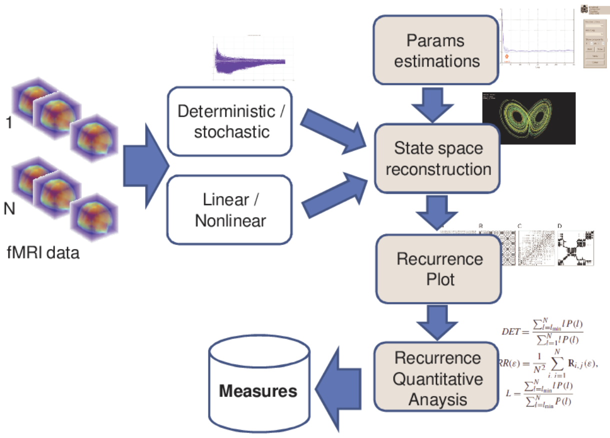


Fig. 1. The algorithm block scheme (details not reported). Figures near the blocks have just illustrative purpose.

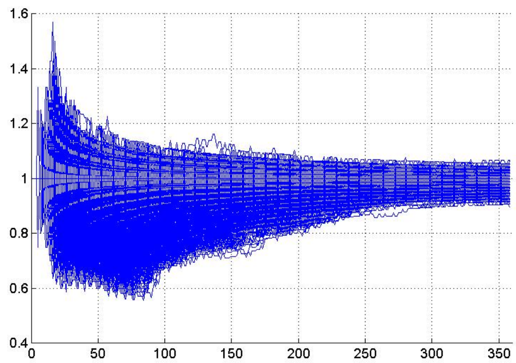


Fig. 2. The LZ complexity measures of 2000 time series of voxels randomly chosen within the brain volume of a healthy subject.

In the Lempel-Ziv complexity measure, the time series is transformed, by quantization, into a finite sequence of symbols and then the number of different sub-strings within it is computed, $c(n)$. This measure reflects the rate of new patterns arising with the increasing of the sequence length. The normalized complexity measure LZ is the current measure divided by its asymptotic trend

$$\begin{aligned} LZ &= c(k)/d(k) \\ d(k) &= \lim_{k\to\infty} c(k) = k/\log_2 k \end{aligned} \quad (1)$$

and tends to zero for a fully deterministic signal and to one for a totally random signal. In Fig. 2 the LZ complexity measure of 2000 voxels randomly taken from the brain volume of a healthy subject clearly shows high complexity behavior. The same trend has been found in other subjects of the study.

To identify nonlinearity in the observed time series X_t

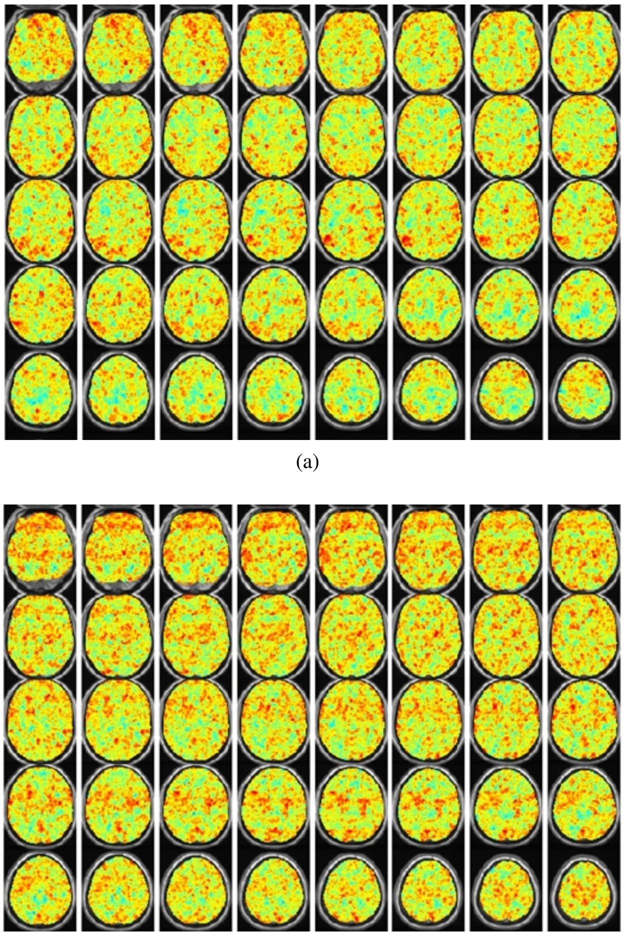
we used an asymptotically unbiased estimate of the third order moment given by

$$\hat{\mu}(r,s) = \frac{1}{n} \sum_{t=1+|\theta|}^{n-\phi} X_t X_{t+r} X_{t+s} \qquad (2)$$

where $\phi = \max(0, r, s)$, $\theta = \min(0, r, s)$ and n is the time series length. The proposed test (see [1] for details) compares the estimated third order moment $\hat{\mu}(r,s)$ of the series with a set of *surrogates*. Surrogates time series are constructed to have the same linear properties (as power spectrum) of the original time series but no other (nonlinear) structure. So, the comparison of high–order statistics measures done on original time series and the surrogates is significantly different and may be detected by a statistical test. The proposed test compares $\hat{\mu}(r,s)$ with a set of limits generated from linear stationary phase scrambled bootstrap data: large differences indicate nonlinearity. We collected, for each voxel, the C-value, i.e. 1 minus the test p-value as a quantification of the rejection rate of the null hypothesis (i.e. the series is linear).

Areas characterized by high nonlinear behavior (i.e. that are statistically significative) are interesting either from an anatomical point of view and for the differences between the two group of subjects. In Fig. 3 the mean C-value is reported for control and patients. For healthy subjects are relevant the activation of areas involved in numerical processing, language comprehension and cross-integration of multisensory information; nonlinear areas are localized in the middle and superior temporal lobe and inferior parietal cortex, in correspondence of the supramarginal gyrus (Wernicke's area). For schizophrenic subjects, instead, we found higher nonlinearity in areas related with visual information such as orbital frontal lobe (supervision of the visual field) and occipital lobe; highly nonlinear areas are located in the occipital lobe and lateral occipito-temporal associated with production of high order visual information. We found also a moderate activation of the insula, where is often located pain sensation and that is active in the processing of sensory information for the production of negative feelings such as discomfort, disgust, etc. Finally, the superior temporal area related to attention and memory tasks is active too.

In principle, determinism or nonlinearity tests are applied at voxel resolution; however, to reduce the level of redundancy and increase the degree of accuracy of the information associated with them, we performed a subdivisions of the nonlinear regions into clusters, that were anatomically relevant. The Density Based Clustering algorithm (DBSCAN) has been applied for each slice of the mean map. DBSCAN basically locates regions of high density that are separated from others by regions of low density. It has several advantages: it uses the concept of noise, is independent of the order of the points in the dataset and determines automatically the number of clusters. Some clusters were automatically generated around areas that are active during task completion, as the parietal cortex (for the WM) or the posterior cingulate cortex or precuneus (for the Default Mode Network, DMN) (see Fig. 4). These clusters were selected for the recurrence analysis; the idea is that the measures on such areas may provide relevant information about the activity during the task.



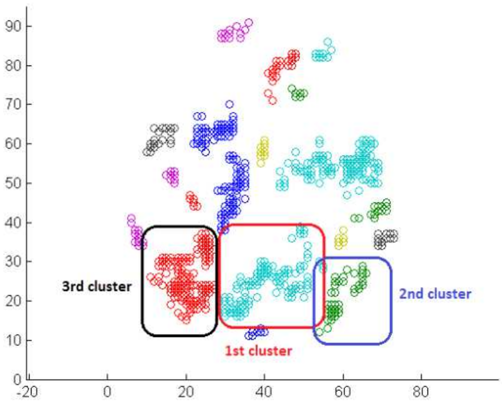
(a)

(b)

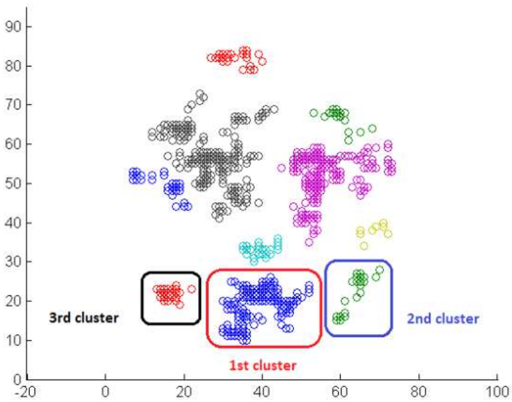
Fig. 3. The mean C-value $\in [0,1]$ among the subjects in the same group for (a) healthy controls, (b) schizophrenic patients for slices going from 17 to 56. The value 1 (deep red) in the scale addresses the highest degree of nonlinearity as result of the statistical test.

C. The Recurrence Plot and RQA

The generation of the RP has been done using the time delay methods, derived from the Takens theorem. This theorem states that it is possible to reconstruct an embedding of a chaotic dynamical system from a sequence of observations of the states. The reconstruction preserves the properties of the dynamical system that do not change under smooth coordinate changes (embedding). The element of novelty and of difficulty in our case is the not-trivial fact



(a)



(b)

Fig. 4. Clusters identified in slice 44 ((a) healthy controls, (b) schizophrenic patients). Some regions of the WM area (as the parietal cortex) can be recognized.

that in fMRI a large set of time series (even in the restricted area of a cluster), spatially related between them, are available. Interpreting a generalization of the embedding theorems [6], we decided to *concatenate* the time series within a cluster to get a robust estimation of the embedding dimension (the False Nearest Neighbors and Cao's algorithms were both used) and time delay (First Zero of Autocorrelation function and First Local Minimum of Average Mutual Information algorithms were used). Optimal time delay τ =2 and embedding dimension m =6 were found; for the embedding dimension we were comforted by the agreement with a previous study [17].

The Recurrence Plot is defined as

$$R_{i,j}(\epsilon) = \Theta\left(\epsilon - ||\mathbf{X}(i) - \mathbf{X}(j)||\right), \qquad i, j = 1, ..., N \tag{3}$$

with $\mathbf{X}(i), \mathbf{X}(j)$ the system state at times i, j, Θ the Heaviside function, $||\cdot||$ a norm and ϵ the degree of neighborhood

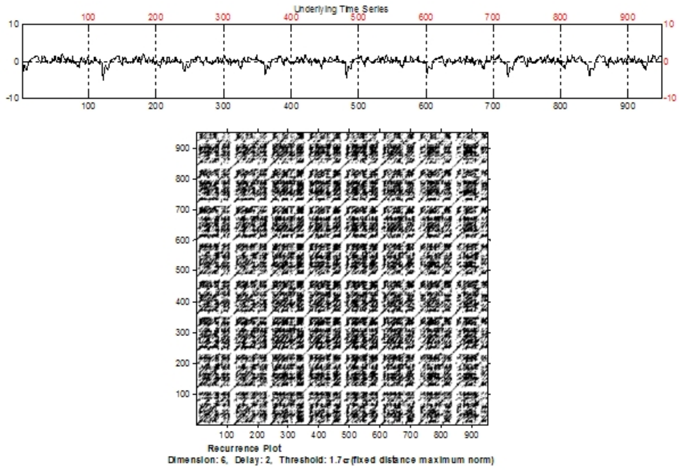


Fig. 5. RP of the time series of a cluster taken from slice 44 and approximately corresponding to the parietal region of a healthy subject.

of the states, expressed by a real and positive number (to be estimated too. We set ϵ as few per cent of the maximum phase state diameter [12]). In principle, a RP may be constructed for each cluster and for each subject. As an example, in Fig. 5 the RP of a cluster approximately corresponding to a WM area (the cluster circled in black in Fig. 4) is shown.

Anyway, in order to go beyond the visual impression, measures of complexity have been proposed to quantify the smallscale structures in the RP that are known as Recurrence Quantification Analysis (RQA). These measures are based on the recurrence point density, diagonal and vertical lines structures of the RP. RQA can be divided into three major classes:

1. Measures based on recurrence density. Among these, the simplest measure is the *recurrence rate*, RR, which is a measure of the density of the recurrence points in the RP.

2. Measures based on the histogram of the diagonal lines. Among these, we focused on the *determinism* D, i.e. the ratio of recurrence points that form diagonal structures to all recurrence points (which is a measure for determinism of the system).

3. Measures based on vertical lines. Among these, we focused on the *trapping time* TT, i.e. the average length of vertical structures. It estimates the mean time that the system will tolerate a specific state or how long the state will be *trapped*. We further collected the *maximal length of vertical lines* $V_{\max}$.

We remark that RQA measures are rather heuristic but describe RPs quantitatively and are helpful to find various transitions in dynamical systems. Some studies show that they are able to identify bifurcation points, especially chaos-order or chaos-chaos transitions, corresponding to the position of the local maxima in the time trend of the *Length of the Longest Vertical Line*. Even if not shown, we found such transitions in our RQA measures: Determinism and Length of the Longest Diagonal Line showed periodic-chaos and chaos periodic transitions; Laminarity, Trapping Time and Length of the Longest Vertical Line exhibited chaos-chaos transitions.

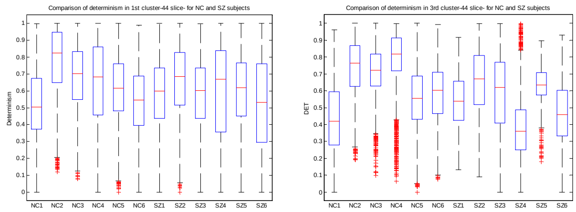
RQA measures are not invariant with respect to the embedding used to reconstruct the phase space trajectory. Anyway, typical invariants in nonlinear dynamics, like generalized entropies (as the Renyi entropy) or dimensions or mutual information, can be inferred from the recurrence matrix. The estimation of the dynamic invariants is not within the scope of this preliminary study and may be matter for future investigation.

The statistical behavior of the time series makes the RQA measures variables with the choice of the time series length, the embedding dimension, the time delay and ϵ. We found that m and τ are quite invariant with the subjects and brain areas, while ϵ change infers on the asymptotic behavior of the RP [12] and so it is relevant for the estimation of the dynamic invariants. For this reason we focused the attention just on the time series length. The computation of RQA measures for moving windows along the whole time series allowed to achieve the time-dependent trend of D, TT and $V_{\max}$.

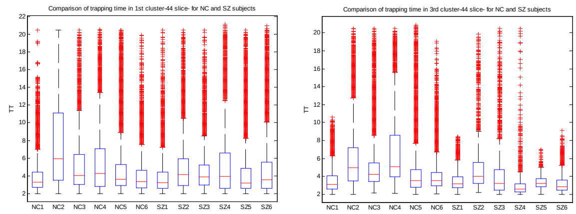
III. RESULTS AND DISCUSSION

Stastistics on Determinism, Trapping Time and Maximal Length of Vertical Lines have been collected and are presented in Fig. 6(a), (b) and (c), respectively and Table 1. In each figure the red line is the position of the median, the edges of the box are the 25^{th} and 75^{th} percentiles, the whiskers extend to the most extreme data points not considered outliers and outliers are plotted individually (red crosses). Figures provide a graphic impression of the differences that exist between the different areas during the task completion and, within the same area, between group of subjects.

In D there is a marked difference between DMN and WM areas, since DMN shows higher standard deviation than the two WM areas for both controls and patients (averages between controls and patients is 0.2238 for DMN area and 0.1647 and 0.1758 for WM areas 2 and 3, respectively). Among groups, instead, schizophrenic patients have a larger variability (slight higher standard deviation and more outliers but lower averages). The mean and standard deviation of TT for patients are both lower than for controls in WM area; moreover DMN area exhibits higher mean and standard deviation than the WM areas. The TT is the average length of the vertical structures in the RP and represents the time interval in which a state does not



(a)



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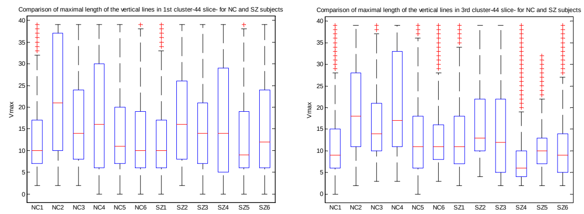

(c)

Fig. 6. (a) D, (b) TT, (c) $V_{\max}$. Left figures: measures from the DMN area (cluster circled in red in Fig. 4); right figures: measures from the WM area (cluster circled in black). NC1,...,NC6 and the controls, SZ1,...,SZ6 are the patients.

change or changes very slowly, a typical behavior of laminar states. Finally, we found that patients have a marked decreased of the mean (and std deviation) of $V_{\max}$ for the WM areas, and, again, DMN presents higher values for both mean and standard deviation with respect to the WM areas.

IV. CONCLUSIONS

In this paper we applied nonlinear basic concepts in the field of brain 4D-mapping, achieved by the functional MRI. fMRI is particularly challenging due to its space-time variability. One of the major difficulty was the selection of the time series from a suitable mask. Nonlinearity test has been used as threshold to select a common mask and then clustering has been applied to group voxels belonging to common functional areas. Applying some hypotheses on generation of the embedded manifold (generalized Takens theorem), nonlinear measures have been found through the RP and RQA techniques. Some qualitative comparison

Table 1. D, TT and $V_{\max}$ mean and standard deviation for healthy and schizophrenic subjects. Values are divided for the three areas identified in Fig. 4.

		Healthy		Schizo	
	Cluster	mean	std	mean	std
D	1-DMN	0.6318	0.2085	0.5912	0.2390
	2-WM	0.6384	0.1602	0.5304	0.1691
	3-WM	0.6407	0.1733	0.5461	0.1783
TT	1-DMN	5.3242	3.4494	4.8302	3.4206
	2-WM	4.4670	2.2590	3.4041	1.0842
	3-WM	5.1965	3.1785	3.7600	1.9061
$V_{\max}$	1-DMN	16.5401	10.9482	15.4520	11.0406
	2-WM	14.9609	9.0887	11.1491	6.3292
	3-WM	15.8681	9.4530	12.2928	7.9246

between the measures seems promising in detecting functional areas or providing discrimination among group of subjects.

However, the work leaves open many issues that deserve in-depth analysis: (i) we still need a more systematic way to select the voxels; (ii) it is as well necessary to identify a systematic description of the useful RQA and which can be adopted for group classification (mental states, disorders, specific task), which for functional areas description; (iii) how to get dynamic invariants and if they can generalize functional description, mental states, subjects or deseases.

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