Applications and extensions of Granger Causality in Neuroimaging: inferences on information flow over the brain.

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ABSTRACT

Vector autoregression (VAR) is one of the most used models to make inferences about relations between time series. Parameters estimation is simple and the interpretation of statistical results is intuitive. In the analysis of fMRI data, Granger causality methods based on VAR estimation have been used to study effective and functional connectivity between brain regions. However, stationarity condition is usually not valid in many real data applications. Furthermore, the BOLD signal measured in fMRI can be influenced by artefacts that may generate spurious correlation between the signals. Finally, the high dimensionality of the data is an obstacle to infer relationships between neural modules. In this paper, we present a review of some approaches developed to tackle these problems. We describe the Dynamic Vector Autoregressive Model based on Wavelets expansion, Partial Directed Coherence Analysis of fMRI data and the Cluster Granger Analysis.

Introduction

Functional magnetic resonance imaging (fMRI) is a modality of neuroimaging that has been widening the exploration of the functioning of human brain in vivo. Basically, several images of the whole brain are acquired over time, allowing a monitoring of the blood oxygenation level dependent (BOLD) signal, measured using the MRI scanner. The BOLD signal is related to haemodynamic coupling and it can be considered an indirect measure of local neuronal activity (Logothetis et al., 2001). The MRI system acquires images of the whole brain (volume) at different time points, and each volume is composed of thousands of voxels (3D units, analogous to pixels in 2D images). Thus, in an fMRI session, thousands of time series measured at different regions of the brain are acquired. The spatial resolution of the voxels is in the scale of millimetres (usually between 3 and 4mm) and the temporal sampling rate is usually between 0.5 to 1Hz.

Several studies in literature use fMRI to identify brain regions that are activated during the presentation of certain stimuli (auditory, visual, emotional, etc) or during the execution of some specific tasks (fingertapping, memorization, etc). However, since the brain is anatomically and functionally organized in an interconnected network, the study of the interactions between different regions at different contexts is extremely important to enhance the comprehension of brain functioning. In addition, the description of information flow in the brain can be crucial to characterize neuropsychiatric disorders, because several diseases are related to disruption in some circuitries.

Granger causality (Granger, 1969) identification using Vector autoregressive (VAR) models is an attractive approach to make inferences on brain connectivity. This concept is related to temporal precedence and conditional distributions, allowing an exploratory analysis of relations between signals, without requiring a priori specification of the network structure.

However, direct application of VAR to fMRI data is limited due to some obstacles. The first one is that inferences using VAR models usually assume data stationarity, which in cases of experiments involving more than one experimental

condition (e.g.: resting vs fingertap) is not satisfied. Another obstacle is that several artefacts such as low frequency oscillations, breath and cardiac rhythms may induce misleading relationships in the data, since they are not related to neural connectivity. In effective connectivity analysis, it is very common to make inferences about the connectivity between some regions of interest (ROI). Each ROI is composed of a set of voxels and the mean time series between these voxels is usually assumed to be the ROI representative. This mean time series is then used to VAR modelling and Granger causality identification. Since the mean may dilute relevant information, this may not be the most sensitive approach to identify the information flow between the ROIs.

In the current paper, some approaches developed to deal with these problems are presented.

Methods

Vector Autoregressive Model

Although Vector Autoregressive (VAR) models are frequently used in Econometrics and time series analysis, Harrison et al. (2003) were the pioneers in applying VAR models for effective connectivity analysis of fMRI data. The main attractive property of VAR is the simplicity on identifying Granger causality. The VAR model of order p for K regions of interest (A, B,…, K) is given by:

$$\begin{cases} A_t = a_{A1}A_{t-1} + \cdots + a_{Ap}A_{t-p} + \cdots + a_{K1}K_{t-1} + \cdots + a_{Kp}K_{t-p} + s_A u_{At} \\ B_t = b_{A1}A_{t-1} + \cdots + b_{Ap}A_{t-p} + \cdots + b_{K1}K_{t-1} + \cdots + b_{Kp}K_{t-p} + s_B u_{Bt} \\ \vdots \\ K_t = k_{A1}A_{t-1} + \cdots + k_{Ap}A_{t-p} + \cdots + k_{K1}K_{t-1} + \cdots + k_{Kp}K_{t-p} + s_K u_{Kt} \end{cases},$$

where u_{*t} are white noise processes with mean zero and variance one. The parameters estimates can be easily obtained by the method of Least Squares or Maximum Likelihood. The Granger causality test for region A on region K can be done by testing whether at least one parameters $k_{A1}, \ldots, k_{Ap}$ is different from zero (using Wald, Score or LR tests). Evaluation of the Granger causality from any other region is analogous. Note that these inferences are based on the temporal precedence of BOLD signals at different

regions. In addition, since Granger causality is not symmetrical, it may suggest the direction of information flow within this network composed of the specified ROIs.

Finally, Goebel et al. (2003) and Abler et al. (2006) have shown that brain connectivity inferences based on VAR models during motor execution are in agreement with literature and results are reproducible in different subjects.

Partial Directed Coherence

As seen in previous subsection, Granger causality relationships of BOLD signals may unveil the underlying influences and interactions between different brain regions. However, since the BOLD signal is not a direct measure of neuronal activity but it is related to haemodynamic coupling, the oscillations of cardiac or breath rhythms may drive common variations in BOLD signal, which may lead to spurious influences when testing Granger causality. In order to overcome this limitation, Sato et al. (2009) suggested the application of partial directed coherence (PDC, Baccala and Sameshima, 2001) for the analysis of fMRI data. The authors also proposed a bootstrap approach for statistical testing in group analysis.

PDC can be seen as a frequency domain version of Granger causality (which is in time domain). The PDC from the *j*-th time series to the *i*-th at frequency λ is defined as:

$$\pi_{ij}(\lambda) = \frac{a_{ij}(\lambda)\dfrac{1}{\sigma_i}}{\sqrt{\sum_{i=1}^{k}\left|a_{ij}(\lambda)\right|^2}},$$

where

$$a_{ij}(\lambda) = \delta_{ij} - \sum_{l=1}^{p} a_{ij}^{(l)} \exp(2\pi i l \lambda),$$

$a_{ij}^{(l)}$ is the autoregressive coefficient of VAR model matrix at row i and column j at lag l, $\delta_{ij} = 1$ if $i = j$ and 0 otherwise. Null PDC values at all frequencies indicate absence of Granger causality and vice-versa.

The squared value of PDC at frequency f can be interpreted as the percentage of energy from area A spectrum at frequency f which is being send to area B. In other words, the PDC decomposes Granger causality in different frequencies. Thus, the influences between regions, which are observed in frequencies which are not related to the experiment, are probably driven by artefacts or components not of interest.

Since most fMRI studies are based on inferences about group of subjects, we are interested in evaluating the significance of the mean PDC (across subjects) at a given frequency. PDC is based on parameters of VAR models, and thus, residuals bootstrap can be applied in this case for both significance testing and obtaining confidence intervals.

In an illustrative verbal fluency experiment, Sato et al. (2009) have shown that PDC were more suitable and powerful than conventional coherence analysis, and it was also useful to identify the direction of information flow at frequencies related to the task execution.

Dynamic Vector Autoregressive model

One of the main limitations of VAR modelling of fMRI data is the stationarity assumption. Except by resting state acquisitions, most fMRI experiments are based on the execution of different tasks or the alternation between different experimental conditions. Thus, it is expected that the influences between the regions of interest to change according to the task being executed. All VAR coefficients are constant in time, implying that the connectivity structure is assumed to be the same independently on the task being executed or the stimuli presented.

In order to overcome this limitation, Sato et al. (2005; 2006) introduced the wavelets based Dynamic Vector Autoregressive Model (DVAR). The basic idea of this model is to assume that the coefficients of VAR models to be functions of time. These functions can then be decomposed using wavelets, and the coefficients of this expansion are estimated using Generalized Least Squares. Theoretical asymptotic properties can be derived assuming local stationarity conditions (Dahlhaus et al., 1999).

The DVAR model is given by

$$\mathbf{y}_t = \mathbf{v}(t) + \mathbf{A}_1(t)\mathbf{y}_{t-1} + \mathbf{A}_2(t)\mathbf{y}_{t-2} + ... + \mathbf{A}_p(t)\mathbf{y}_{t-p} + \mathbf{u}_t,$$

where $\mathbf{u}_t$ is a random error vector of null mean and covariance matrix

$$\bar{\mathbf{I}}(t) = \begin{bmatrix} \sigma_{11}^2(t) & \sigma_{21}(t) & \cdots & \sigma_{k1}(t) \\ \sigma_{12}(t) & \sigma_{22}^2(t) & \cdots & \sigma_{k2}(t) \\ \sigma_{13}(t) & \sigma_{23}(t) & \cdots & \sigma_{k3}(t) \\ \vdots & \vdots & \ddots & \vdots \\ \sigma_{1k}(t) & \sigma_{2k}(t) & \cdots & \sigma_{kk}^2(t) \end{bmatrix},$$

and $\mathbf{v(t)}$ and $\mathbf{A}_i$(t) ($i=1,2,...,p$) are coefficient matrices

$$\mathbf{v}(t) = \begin{bmatrix} v_1(t) \\ v_2(t) \\ \vdots \\ v_k(t) \end{bmatrix} \qquad \mathbf{A}_i(t) = \begin{bmatrix} a_{11i}(t) & a_{21i}(t) & \cdots & a_{k1i}(t) \\ a_{12i}(t) & a_{22i}(t) & \cdots & a_{k2i}(t) \\ a_{13i}(t) & a_{23i}(t) & \cdots & a_{k3i}(t) \\ \vdots & \vdots & \ddots & \vdots \\ a_{1ki}(t) & a_{2ki}(t) & \cdots & a_{kki}(t) \end{bmatrix}.$$

The main idea of DVAR based on wavelet expansion is to decompose all functions from previous matrix as

$$a_{lmi}(t) = c_{-1,0}^{(i)}\phi(t) + \sum_{j=0}^{J}\sum_{k=0}^{2^j-1} c_{j,k}^{(i)}\psi_{jk}(t).$$

where $\phi(t)$ is the scale function and $c_{j,k}^{(i)}$ *(j=-1,0,1,...T-1 ; k=0,1,2,...,2^j-1 ; i=1,2,...p)* are the wavelet coefficients of the i-th autoregressive coefficient function $a_{lmi}(t)$. In this expansion, the wavelets functions $\phi(t)$ and $\psi_{jk}(t)$ are defined a priori. Sato et al. (2005; 2006) have shown that by using this approximation, the DVAR model can be written as a particular case of the general linear model.

In addition, Sato et al. (2005) has derived the asymptotic distribution of the estimators, showing normality and consistency. The authors have also shown, by using computational simulations, that these properties can be accurately approximated in case of large samples. Finally, they have illustrated the application of this model in real fMRI datasets, showing that the connectivity of motor system and parietal regions changes when the subject alternates between resting state and fingertapping conditions.

Cluster Granger Analysis

Another important limitation in all ROI analysis of MRI data is that the ROIs are composed of several voxels at each brain region. This means that within a region, there are several time series at different voxels. In most cases, the average time series (across voxels at each timepoint) or the first principal component is assumed to be the ROI representative. All connectivity analyses are then carried out using these regional representative signals. However neither the average nor the 1st PCA are taking into account the predictive power of lagged valued. Thus, relevant temporal information may be diluted when averaging these signals.

In order to deal with this problem, Sato et al. (2010) have proposed the Cluster Granger Analysis (CGA) of fMRI data. This approach is a combination of multivariate methods focusing on the identification of Granger causality between sets of time series. CGA pipeline is composed of the following steps:

1. Define the voxels representing each region of interest;
2. Obtain principal components from the BOLD signals at each ROI. Select the components contributing more than 5% of the data variance;
3. Apply Partial Canonical Correlation Analysis (PCCA) in order to evaluate whether the past values of each ROI can be used to predict the current values of the others.
4. Apply bootstrap to approximate the p-values of Granger causality tests.

The mathematical foundation of CGA can be found in detail on Sato et al. (2010). By using computational simulations, the authors have shown that CGA is indeed more

powerful than Granger causality tests based on VAR models assuming the mean (and 1st PCA) BOLD signal of each ROI as the region representative. Finally, the authors applied CGA in real fMRI dataset from an experiment involving the presentation of faces with sadness valence. In this analysis, CGA identified more connections than conventional VAR analysis, for the same level of Type I Error.

Discussion

Neuroscience literature describe that the brain is anatomically and functionally organized in a complex network. This organization implies that multivariate analysis of brain signals is necessary to enhance the knowledge about cognitive processing. Because its simplicity and exploratory description, Granger causality concept has become an important tool regarding the inferences about information flow between brain regions.

Although the presented approaches were developed to tackle some obstacles to the use of Granger causality in fMRI data, there are still open and major problems. The main limitation is related to the nature of the BOLD signal, which is not a direct measure of brain activity. The main focus of connectivity analysis is to make inferences about neural networks, but an inherent obstacle is that the signals observed are related to haemodynamic coupling. Thus, local haemodynamic parameters or process may influence or mask the results. This means that caution is necessary when interpreting Granger causality inferences. Some authors have proposed deconvolution models to reduce the effects of haemodynamics, but the solution is still an open question.

Future perspectives point towards the development of connectivity approaches to deal with signals from multimodal acquisition, such as simultaneous EEG-fMRI or EEG-NIRS. The main concern is the integration of information at different spatial/temporal resolution from electric/metabolic measurements.

Acknowledgements

This study was supported by FAPESP Brazil.

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